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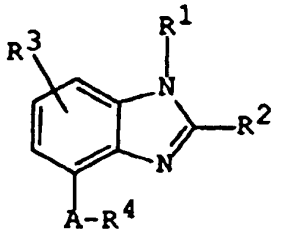
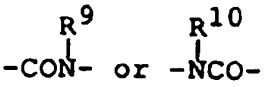
(57) Abstract

The present invention relates to a new heterocyclic compound of formula (I), wherein R^1 is acyl, lower alkenyl or lower alkyl optionally substituted with aryl, a heterocyclic group, etc., R^2 is hydrogen, lower alkyl, hydroxy(lower)alkyl, halo(lower)alkyl, etc., R^3 is hydrogen or halogen, R^4 is a heterocyclic group or aryl, each of which may be substituted with suitable substituent(s), and A is (a) or (b), (wherein R^9 and R^{10} are each hydrogen, lower alkyl or substituted lower alkyl), and pharmaceutically acceptable salts thereof which are the inhibitors of bone resorption and bone metabolism, to processes for preparation thereof, to a pharmaceutical composition comprising the same and to a method for the treatment of diseases caused by abnormal bone metabolism in human being or an animal.



(I)



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D E S C R I P I O N

BENZIMIDAZOLE DERIVATIVES AND THEIR USE IN THE PREVENTION AND/OR THE TREATMENT OF BONE DISEASES

TECHNICAL FIELD

This invention relates to new heterocyclic compounds and pharmaceutically acceptable salts thereof.

More particularly, it relates to new heterocyclic compounds and pharmaceutically acceptable salts thereof which are the inhibitors of V-type H^+-ATPase, especially osteoclast H^+-ATPase, the inhibitors of bone resorption, the inhibitors of bone metastasis and useful for the prevention and/or the treatment of bone diseases caused by abnormal bone metabolism in human being or animals.

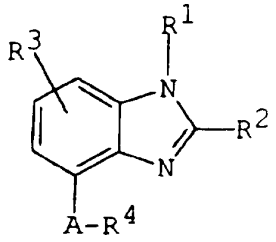
And further, the present invention relates to processes for the preparation of said compounds, to a pharmaceutical composition comprising the same and to a method for the prevention and/or the treatment of above-mentioned diseases in human being or animals, and to a use of said compounds and pharmaceutically acceptable salts thereof for the prevention and/or the treatment of above-mentioned diseases in human being or animals.

BACKGROUND ART

Some heterocyclic compounds have been known as described, for example, in EP-A-574,174, Chemical Abstracts 100:133915g (1984), Chemical Abstracts 98:175462c (1983) or Chemical Abstracts 97:49315y (1982). However, it is not known that said compounds are useful for the prevention and/or the treatment of above-mentioned diseases.

DISCLOSURE OF INVENTION

The object heterocyclic compounds of this invention are new and can be represented by the following general formula [I] :



[I]

wherein

R^1 is acyl, lower alkenyl or lower alkyl optionally substituted with substituent(s) selected from the group consisting of aryl, substituted aryl, a heterocyclic group, a substituted heterocyclic group, hydroxy, substituted hydroxy, cyano, halogen, amino, substituted amino, acyl, mercapto, substituted mercapto, hydroxyamidino, substituted hydroxyamidino and substituted hydrazono, and

R^2 is hydrogen, lower alkyl, hydroxy(lower)alkyl, halo(lower)alkyl, lower alkoxy, lower alkylthio, acyl or cyano, or

R^1 and R^2 are taken together to form lower alkylene or lower alkenylene, each of which may include O, S or N-R^5 in the chain, in which R^5 is hydrogen or lower alkyl,

R^3 is hydrogen or halogen,

R^4 is a heterocyclic group or aryl, each of which may be substituted with suitable substituent(s), and

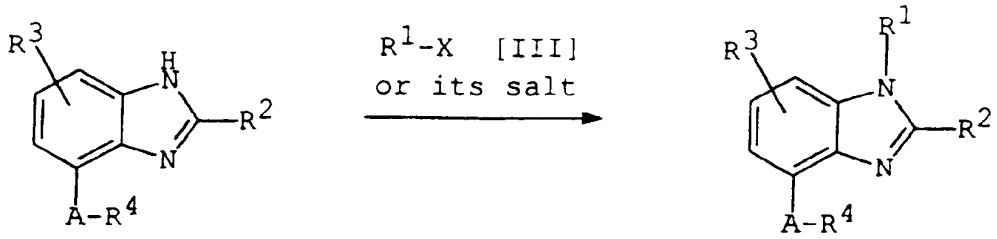
A is $-CON(R^9)-$ or $-N(R^{10})CO-$,

in which R^9 is hydrogen, lower alkyl or substituted lower alkyl, and

R^{10} is hydrogen, lower alkyl or substituted lower alkyl.

The object compound [I] or its salt can be prepared by processes as illustrated in the following reaction schemes.

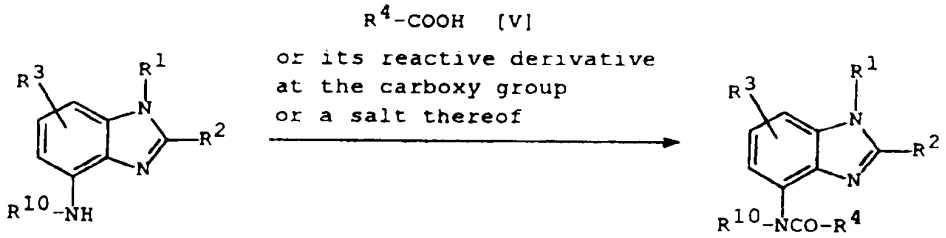
Process 1



[II]
or its salt

[I]
or its salt

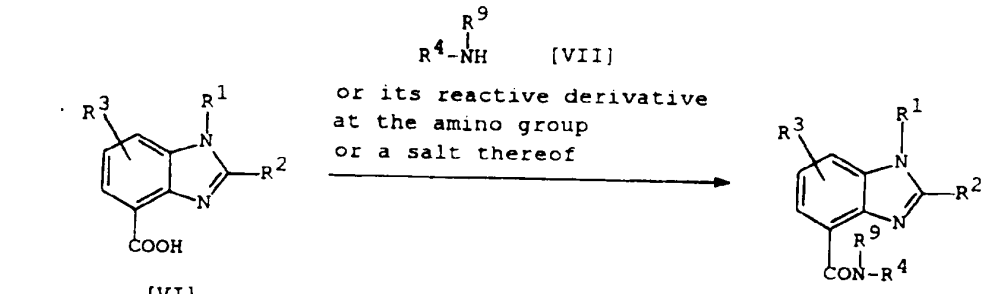
Process 2



[IV]
or its reactive derivative
at the amino group or
a salt thereof

[Ia]
or its salt

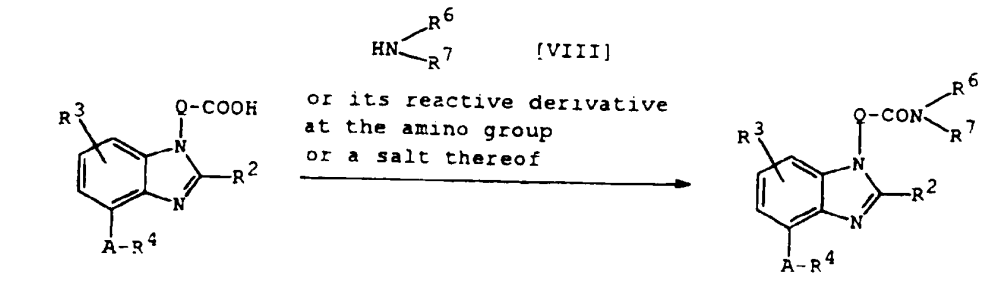
Process 3



[VI]
or its reactive derivative
at the carboxy group
or a salt thereof

[Ib]
or its salt

Process 4



[Ic]
or its reactive derivative
at the carboxy group
or a salt thereof

[Id]
or its salt

wherein

R^6 is hydrogen or lower alkyl optionally substituted with a substituent selected from the group consisting of hydroxy and lower alkoxy, and

R^7 is hydrogen; acyl; lower alkoxy; amino; acylamino; aryl optionally substituted with a substituent selected from the group consisting of lower alkoxy, halo(lower)alkyl and lower alkylamino; a heterocyclic group optionally substituted with a substituent selected from the group consisting of lower alkyl, lower alkoxy, lower alkylthio, halo(lower)alkyl and acyl; or lower alkyl optionally substituted with substituent(s) selected from the group consisting of hydroxy, lower alkoxy, halogen, cyano, acyloxy, acyl, aryl optionally having halo(lower)alkyl and a heterocyclic group optionally having lower alkyl; or

R^6 and R^7 are taken together with the attached nitrogen atom to form a heterocyclic group optionally substituted with a substituent selected from the group consisting of lower alkyl, halogen, aryl and acyl,

Q is lower alkylene,

X is a leaving group, and

R^1, R^2, R^3, R^4, R^9, R^{10} and A are each as defined above.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

In this respect, the term "lower" in lower alkenyl moiety in the various definitions is intended to mean a group having 2 to 6 carbon atoms.

Further, the term "lower" in cyclo(lower)alkyl moiety in

the various definitions is intended to mean a group having 3 to 6 carbon atoms.

Suitable "acyl" and all acyl moieties in the various definitions mentioned in this specification and claims such as in the term "acylamino", "acyloxy", etc. may be substituted or unsubstituted lower alkanoyl such as lower alkanoyl [e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, 3,3-dimethylbutyryl, etc.], halo(lower)alkanoyl [e.g. chloroacetyl, trifluoroacetyl, bromoacetyl, bromobutyryl, heptafluorobutyryl, etc.], hydroxy(lower)alkanoyl [e.g. glycoloyl, lactoyl, 3-hydroxypropionyl, glyceroyl, etc.], lower alkylsulfonyloxy(lower)alkanoyl [e.g. mesyloxyacetyl, ethylsulfonyloxyacetyl, mesyloxypropionyl, etc.], lower alkoxy(lower)alkanoyl [e.g. methoxyacetyl, ethoxyacetyl, methoxypropionyl, ethoxypropionyl, propoxypropionyl, methoxybutyryl, etc.], carboxy(lower)alkanoyl [e.g. oxalo, carboxyacetyl, 3-carboxypropionyl, 3-carboxybutyryl, 4-carboxybutyryl, 4-carboxyvaleryl, etc.], esterified carboxy(lower)alkanoyl, for example, lower alkoxycarbonyl(lower)alkanoyl [e.g. methoxycarbonylacetyl, ethoxycarbonylacetyl, methoxycarbonylpropionyl, etc.], succinimidooxycarbonyl(lower)alkanoyl [e.g. succinimidooxycarbonylbutyryl, etc.], carbamoyl(lower)alkanoyl [e.g. carbamoylacetyl, carbamoylpropionyl, etc.], lower alkylcarbamoyl(lower)alkanoyl [e.g. methylcarbamoylacetyl, ethylcarbamoylpropionyl, dimethylcarbamoylpropionyl, etc.], diphosphono(lower)alkylcarbamoyl(lower)alkanoyl [e.g. diphosphonomethylcarbamoylbutyryl, etc.], ar(lower)alkanoyl [e.g. phenylacetyl, tolylacetyl, naphthylacetyl, etc.], optionally substituted heterocyclic(lower)alkanoyl [e.g. morpholinoacetyl, thiomorpholinopropionyl, piperazinylpropionyl, pyridylacetyl, imidazolidinylpropionyl, piperidinoacetyl, pyrrolidinylacetyl,

hexamethyleneiminoacetyl, imidazolylacetyl, furylacetyl, thienylacetyl, methylpiperazinylacetyl, pyridylpiperazinylacetyl, etc.], etc., cyclo(lower)alkylcarbonyl [e.g. cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.], carboxy, esterified carboxy such as lower alkoxycarbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.], aryloxycarbonyl [e.g. phenoxycarbonyl, etc.], etc., substituted or unsubstituted aroyl such as aroyl [e.g. benzoyl, toluoyl, xyloyl, naphthoyl, etc.], lower alkoxyaroyl [e.g. methoxybenzoyl, etc.], haloaroyl [e.g. chlorobenzoyl, fluorobenzoyl, dichlorobenzoyl, etc.], acylaroyl, for example, lower alkoxycarbonylaroyl [e.g. methoxycarbonylbenzoyl, etc.], etc., heterocycliccarbonyl which may be substituted with substituent [e.g. furoyl, thenoyl, pyridylcarbonyl, morpholinocarbonyl, piperidinocarbonyl, 4-methyl-1-piperazinylcarbonyl, 4-ethyl-1-piperazinylcarbonyl, dimethylaminopiperidinocarbonyl, 4-methylcarbamoyl-1-piperazinylcarbonyl, 4-acetyl-1-piperazinylcarbonyl, 4-phenyl-1-piperazinylcarbonyl, chlorothenoyl, 1,2,3,6-tetrahydropyridylcarbonyl, pyrrolidinylcarbonyl, indolylcarbonyl, etc.], aryloxycarbonyl which may be substituted with nitro [e.g. phenyloxycarbonyl, nitrophenyloxycarbonyl, etc.], ar(lower)alkoxycarbonyl which may be substituted with nitro [e.g. benzyloxycarbonyl, nitrobenzyloxycarbonyl, etc.], substituted or unsubstituted carbamoyl such as carbamoyl, lower alkylcarbamoyl [e.g. methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, isobutylcarbamoyl, tert-butylcarbamoyl, pentylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, N-ethyl-N-methylcarbamoyl, etc.], carboxy(lower)alkylcarbamoyl [e.g. carboxymethylcarbamoyl,

carboxyethylcarbamoyl, etc.], esterified carboxy(lower)alkylcarbamoyl, for example, lower alkoxycarbonyl(lower)alkylcarbamoyl [e.g. methoxycarbonylmethylcarbamoyl, ethoxycarbonylmethylcarbamoyl, ethoxycarbonylethylcarbamoyl, etc.], lower alkenylcarbamoyl [e.g. vinylcarbamoyl, allylcarbamoyl, etc.], cyclo(lower)alkylcarbamoyl [e.g. cyclopropylcarbamoyl, cyclobutylcarbamoyl, cyclopentylcarbamoyl, cyclohexylcarbamoyl, etc.], halo(lower)alkylcarbamoyl [e.g. chloromethylcarbamoyl, trifluoromethylcarbamoyl, trifluoroethylcarbamoyl, etc.], cyano(lower)alkylcarbamoyl [e.g. cyanomethylcarbamoyl, etc.], hydroxy(lower)alkylcarbamoyl [e.g. hydroxyethylcarbamoyl, hydroxypropylcarbamoyl, di(hydroxyethyl)carbamoyl, dihydroxypropylcarbamoyl, 1,1-dimetyl-2-hydroxyethylcarbamoyl, etc.], lower alkoxy(lower)alkylcarbamoyl [e.g. methoxyethylcarbamoyl, methoxypropylcaramoyl, di(methoxyethyl)carbamoyl, etc.], lower alkanoyloxy(lower)alkylcarbamoyl [e.g. acetoxyethylcarbamoyl, acetoxypropylcarbamoyl, diacetoxypropylcarbamoyl, etc.], lower alkoxycarbamoyl [e.g. methoxycarbamoyl, ethoxycarbamoyl, etc.], protected or unprotected aminocarbamoyl [e.g. aminocarbamoyl, tert-butoxycarbonylaminocarbamoyl, etc.], carbamoyl(lower)alkylcarbamoyl [e.g. carbamoylmethylcarbamoyl, carbamoylethylcarbamoyl, etc.], hydroxy(lower)alkylcarbamoyl(lower)alkylcarbamoyl [e.g. hydroxyethylcarbamoylmethylcarbamoyl, hydroxyethylcarbamoylethylcarbamoyl, etc.], arylsulfonylcarbamoyl [e.g. phenylsulfonylcarbamoyl, tosylcarbamoyl, etc.], substituted or unsubstituted arylcarbamoyl, for example, arylcarbamoyl [e.g. phenylcarbamoyl, tolylcarbamoyl, xylylcarbamoyl, naphthylcarbamoyl, ethylphenylcarbamoyl, etc.], lower alkoxy-arylcarbamoyl [e.g. methoxyphenylcarbamoyl, etc.],

halo-arylcarbamoyl [e.g. fluorophenylcarbamoyl, chlorophenylcarbamoyl, etc.], halo(lower)alkyl-arylcarbamoyl [e.g. trifluoromethylphenylcarbamoyl, etc.], nitro-arylcarbamoyl [e.g. nitrophenylcarbamoyl, etc.], cyano-arylcarbamoyl [e.g. cyanophenylcarbamoyl, etc.], hydroxy(lower)alkyl-arylcarbamoyl [e.g. hydroxymethylphenylcarbamoyl, hydroxyethylphenylcarbamoyl, etc.], amino-arylcarbamoyl [e.g. aminophenylcarbamoyl, etc.], lower alkylamino-arylcarbamoyl [e.g. methylaminophenylcarbamoyl, ethylaminophenylcarbamoyl, dimethylaminophenylcarbamoyl, etc.], lower alkanoylamino-arylcarbamoyl [e.g. acetylaminophenylcarbamoyl, propionylaminophenylcarbamoyl, etc.], etc., substituted or unsubstituted ar(lower)alkylcarbamoyl, for example, ar(lower)alkylcarbamoyl [e.g. benzylcarbamoyl, phenethylcarbamoyl, etc.], halo(lower)alkyl-ar(lower)alkylcarbamoyl [e.g. trifluoromethylbenzylcarbamoyl, etc.], etc., substituted or unsubstituted heterocyclic(lower)alkylcarbamoyl, for example, heterocyclic(lower)alkylcarbamoyl [e.g. pyridylmethylcarbamoyl, pyridylethylcarbamoyl, oxadiazolylmethylcarbamoyl, furylmethylcarbamoyl, thienylmethylcarbamoyl, tetrahydrofurylmethylcarbamoyl, piperonylcarbamoyl, piperonylmethylcarbamoyl, indolylethylcarbamoyl, imidazolylethylcarbamoyl, etc.], lower alkyl-heterocyclic(lower)alkylcarbamoyl [e.g. methylpyridylmethylcarbamoyl, methyloxadiazolylmethylcarbamoyl, etc.], etc., substituted or unsubstituted heterocycliccarbamoyl, for example, heterocycliccarbamoyl [e.g. furylcarbamoyl, thienylcarbamoyl, pyridylcarbamoyl, quinolylcarbamoyl, isoquinolylcarbamoyl, pyrimidinylcarbamoyl, pyrazolylcarbamoyl, morpholinocarbamoyl, thiazolylcarbamoyl, oxazolylcarbamoyl, isoxazolylcarbamoyl, thiadiazolylcarbamoyl, etc.], lower alkyl-

heterocycliccarbamoyl [e.g. methylpyridylcarbamoyl, methyloxazolylcarbamoyl, methylisoxazolylcarbamoyl, methylthiadiazolylcarbamoyl, etc.], halo(lower)alkyl-heterocycliccarbamoyl [e.g. trifluoromethylpyridylcarbamoyl, trifluoromethylthiadiazolylcarbamoyl, etc.], lower alkoxy-heterocycliccarbamoyl [e.g. methoxypyridylcarbamoyl, methoxythiadiazolylcarbamoyl, etc.], lower alkylthio-heterocycliccarbamoyl [e.g. methylthiopyridylcarbamoyl, ethylthiothiadiazolylcarbamoyl, etc.], sulfamoyl-heterocycliccarbamoyl [e.g. sulfamoylthiadiazolylcarbamoyl, etc.], etc., N-heterocyclic-N-(lower alkyl)carbamoyl [e.g. N-pyridyl-N-methylcarbamoyl, N-thiazolyl-N-methylcarbamoyl, etc.], etc., lower alkylsulfonyl [e.g. mesyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, tert-butylsulfonyl, pentylsulfonyl, etc.], arylsulfonyl [e.g. tosyl, phenylsulfonyl, etc.], ar(lower)alkylsulfonyl [e.g. benzylsulfonyl, phenethylsulfonyl, etc.], ar(lower)alkenylsulfonyl [e.g. styrylsulfonyl, cinnamylsulfonyl, etc.], phthaloyl, or the like.

Suitable "lower alkenyl" may be vinyl, allyl, methylpropenyl, butenyl, pentenyl or the like.

Suitable "lower alkyl" and lower alkyl moiety in the terms "heterocyclic(lower)alkyl", "hydroxy(lower)alkyl", "lower alkylthio" and "lower alkylamino" may be straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl or the like, in which preferable one is C_1-C_4 alkyl such as methyl, ethyl, propyl, isobutyl or tert-butyl.

Suitable "aryl" may be phenyl, naphthyl, phenyl substituted with lower alkyl [e.g. tolyl, xylyl, mesityl, cumenyl, di(tert-butyl)phenyl, etc.] and the like, in which preferable one is phenyl, naphthyl and tolyl.

Suitable "heterocyclic group" and all heterocyclic moieties in the various definitions mentioned in this specification and claims such as in the term

"heterocyclic(lower)alkyl", "heterocycliccarbonyl", etc., may include saturated or unsaturated, monocyclic or polycyclic one containing at least one hetero atom such as nitrogen atom, oxygen atom or sulfur atom, preferably N, O and/or S containing heterocyclic group, in which preferable ones may be morpholinyl, piperazinyl, pyridyl, tetrahydropyridyl, pyrimidinyl, piperidyl, thienyl, furyl, oxazolyl, isoxazolyl, thiazolyl, thiazolinyl, oxadiazolyl, dihydrooxadiazolyl, thiadiazolyl, tetrazolyl, imidazolyl, imidazolidinyl, pyrrolidinyl, pyrrolyl, oxiranyl, tetrahydrofuryl, piperonyl, indolyl, quinolyl, isoquinolyl, imidazopyridyl, benzodioxolyl, phthalimido, or the like.

Suitable "halogen" may be fluorine, chlorine, bromine and iodine.

Suitable "halo(lower)alkyl" may be chloromethyl, bromoethyl, dichloromethyl, difluoromethyl, trifluoromethyl, or the like.

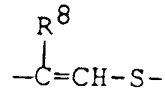
Suitable "lower alkoxy" may be straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy or the like, in which preferable one is C_1-C_4 alkoxy such as methoxy, ethoxy or isopropoxy.

Suitable "lower alkylene" may be a straight or branched one such as methylene, ethylene, trimethylene, methylmethylene, tetramethylene, ethylethylene, propylene, pentamethylene, hexamethylene or the like, in which the most preferable one is methylene.

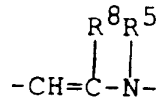
Suitable "lower alkenylene" may be a straight or branched C_2-C_6 alkenylene such as vinylene, methylvinylene, propenylene, 1,3-butadienylene or the like, in which the most preferable one is vinylene.

Preferable lower alkylene or lower alkenylene, each of which includes O, S or N-R^5 in the chain formed by R^1 and R^2 may be a group of the formula :

$-CH_2-CH_2-CH_2-S-$,



$-CH_2-CH_2-CH_2-O-$,



in which R^8 is hydrogen or lower alkyl and
R^5 is as defined above,
or the like.

Suitable substituents of aryl in the term "substituted aryl" may be nitro, cyano, the above-mentioned lower alkoxy or the above-mentioned halo(lower)alkyl, or the like.

Suitable substituents of a heterocyclic group in the term "a substituted heterocyclic group" may be oxo, the above-mentioned lower alkyl, the above-mentioned halogen, the above-mentioned heterocyclic group, or the like.

Suitable substituents of hydroxy in the term "substituted hydroxy" may be the above-mentioned lower alkyl, the above-mentioned acyl, the above-mentioned aryl, the above-mentioned a heterocyclic group, ar(lower)alkyl such as phenyl(lower)alkyl [e.g. benzyl, phenethyl, phenylpropyl, etc.] or the like.

Suitable substituents of amino in the term "substituted amino" may be the above-mentioned acyl, or the like.

Suitable substituents of mercapto in the term

"substituted mercapto" may be the above-mentioned a heterocyclic group which may be substituted by the above-mentioned lower alkyl; the above-mentioned aryl; or the like.

Suitable substituents of hydroxyamidino in the term "substituted hydroxyamidino" may be the above-mentioned acyl.

Suitable substituents of hydrazono in the term "substituted hydrazono" may be the above-mentioned lower alkyl, the above-mentioned a heterocyclic group, or the like.

Suitable substituents in the term "a heterocyclic group or aryl, each of which may be substituted with suitable substituent(s)" for R^4 may be the above-mentioned halogen; the above-mentioned lower alkyl; hydroxy(lower)alkyl; the above-mentioned lower alkoxy; lower alkoxy(lower)alkoxy; the above-mentioned halo(lower)alkyl; halo(lower)alkoxy; nitro; amino optionally substituted with lower alkyl or acyl; the above-mentioned aryl; the above-mentioned acyl; lower alkoxycarbonyl(lower)alkenyl; hydroxy(lower)alkyl optionally substituted with lower alkyldiarylsilyl; or the like, in which preferable ones are halogen, lower alkyl or lower alkoxy.

Suitable "heterocyclic group" formed by R^6, R^7 and the attached nitrogen atom may be morpholino, thiomorpholino, pyrrolidin-1-yl, piperidino, 1,2,3,6-tetrahydropyridin-1-yl, piperazin-1-yl, or the like.

Suitable substituents of lower alkyl in the term "substituted lower alkyl" for R^9 and R^{10} may be the above-mentioned acyl.

Suitable "a leaving group" may be a conventional acid residue such as halogen [e.g. fluoro, chloro, bromo and iodo], arenesulfonyloxy [e.g. benzenesulfonyloxy, tosyloxy, etc.], alkanesulfonyloxy [e.g. mesyloxy, ethanesulfonyloxy, etc.], and the like.

Suitable pharmaceutically acceptable salts of the object compound [I] are conventional non-toxic salts and include a metal salt such as an alkali metal salt [e.g. sodium salt,

potassium salt, etc.] and an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.], an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, oxalate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], a salt with an amino acid [e.g. arginine salt, aspartic acid salt, glutamic acid salt, etc.], an intramolecular salt and the like.

With respect to the salts of the compounds [Ia] to [Id] in the Processes 2 to 4, it is to be noted that those compounds are included within the scope of the compound [I], and accordingly the suitable examples of the salts of these compounds are to be referred to those as exemplified for the object compound [I].

Preferred embodiments of the object compound [I] are as follows :

R^1 is lower alkanoyl; haloaroyl; lower alkenyl; lower alkyl; or lower alkyl substituted with substituent(s) selected from the group consisting of aryl, aryl substituted with nitro, aryl substituted with cyano, aryl substituted with lower alkoxy, a heterocyclic group, a heterocyclic group substituted with a heterocyclic group, a heterocyclic group substituted with lower alkyl, a heterocyclic group substituted with halogen, a heterocyclic group substituted with one or two oxo(s), hydroxy, hydroxy substituted with lower alkyl, hydroxy substituted with acyl [more preferably hydroxy substituted with lower alkanoyl, hydroxy substituted with carboxy(lower)alkanoyl, hydroxy substituted with

succinimidooxycarbonyl(lower)alkanoyl, hydroxy substituted with diphosphono(lower)alkylcarbamoyl-(lower)alkanoyl, hydroxy substituted with aryl, hydroxy substituted with ar(lower)alkyl, hydroxy substituted with a heterocyclic group, etc.], cyano, halogen, amino, acylamino [more preferably lower alkanoylamino, lower alkylsulfonylamino, heterocycliccarbonylamino, etc.], acyl [more preferably lower alkanoyl, aroyl, carboxy, lower alkoxycarbonyl, heterocycliccarbonyl, heterocycliccarbonyl substituted with lower alkyl, heterocycliccarbonyl substituted with lower alkanoyl, heterocycliccarbonyl substituted with halogen, heterocycliccarbonyl substituted with aryl, carbamoyl, lower alkylcarbamoyl, carboxy(lower)alkylcarbamoyl, lower alkoxycarbonyl(lower)alkylcarbamoyl, cyclo(lower)alkylcarbamoyl, halo(lower)alkylcarbamoyl, cyano(lower)alkylcarbamoyl, hydroxy(lower)-alkylcarbamoyl, lower alkoxy(lower)alkylcarbamoyl, lower alkanoyloxy(lower)alkylcarbamoyl, lower alkoxycarbamoyl, aminocarbamoyl, tert-butoxycarbonylaminocarbamoyl, carbamoyl(lower)alkylcarbamoyl, hydroxy(lower)alkylcarbamoyl(lower)alkylcarbamoyl, arylsulfonylcarbamoyl, arylcarbamoyl, lower alkoxy-arylcarbamoyl, halo(lower)alkyl-arylcarbamoyl, lower alkylamino-arylcarbamoyl, ar(lower)alkylcarbamoyl, halo(lower)alkyl-ar(lower)alkylcarbamoyl, heterocyclic-(lower)alkylcarbamoyl, lower alkyl-heterocyclic(lower)-alkylcarbamoyl, heterocycliccarbamoyl, lower alkyl-heterocycliccarbamoyl, halo(lower)alkyl-heterocycliccarbamoyl, lower alkoxy-heterocycliccarbamoyl, lower alkylthio-heterocycliccarbamoyl, sulfamoyl-heterocycliccarbamoyl, N-heterocyclic-N-(lower alkyl)carbamoyl, phthaloyl, etc.], mercapto, mercapto

substituted with a heterocyclic group, mercapto substituted with a heterocyclic group substituted with lower alkyl, hydroxyamidino, hydroxyamidino substituted with acyl [more preferably hydroxyamidino substituted with lower alkoxycarbonyl], and hydrazono substituted with a heterocyclic group; and

R^2 is hydrogen, lower alkyl, hydroxy(lower)alkyl, halo(lower)alkyl, lower alkoxy, lower alkylthio, lower alkylsulfonyl, carbamoyl or cyano, in which more preferable ones are lower alkyl, halo(lower)alkyl or cyano, or

R^1 and R^2 are taken together to form a group of the formula :

$$-CH_2-CH_2-CH_2-S-,$$

$$-\overset{R^8}{\overset{|}{C}}=CH-S-,$$

$$-CH=\overset{R^8}{\overset{|}{C}}-\overset{R^5}{\overset{|}{N}}-,$$

in which R^5 and R^8 are each hydrogen or lower alkyl,

R^3 is hydrogen or halogen,

R^4 is aryl substituted with substituent(s) selected from the group consisting of halogen, lower alkyl, lower alkoxy, lower alkoxy(lower)alkoxy, halo(lower)alkoxy, lower alkanoyl, lower alkoxycarbonyl(lower)alkenyl, hydroxy(lower)alkyl and lower alkyldiarylsilyloxy-(lower)alkyl, and

A is $-\overset{R^9}{\overset{|}{C}}O-$ or $-\overset{R^{10}}{\overset{|}{N}}CO-$,

in which R^9 is hydrogen, lower alkyl or lower alkoxycarbonyl(lower)alkyl, and

R^{10} is hydrogen, lower alkyl or lower alkoxycarbonyl(lower)alkyl.

The processes for preparing the object compound [I] are explained in detail in the following.

Process 1

The object compound [I] or its salt can be prepared by reacting a compound [II] or its salt with a compound [III] or its salt.

Suitable salts of the compounds [II] and [III] may be the same as those exemplified for the compound [I].

The reaction is preferably carried out in the presence of a base such as alkali metal [e.g. lithium, sodium, potassium, etc.], the hydroxide or carbonate or bicarbonate thereof [e.g. sodium hydroxide, potassium carbonate, potassium bicarbonate, etc.], alkali metal alkoxide [e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.], triethylamine, or the like.

This reaction is usually carried out in a conventional solvent such as tetrahydrofuran, dioxane, dichloromethane, ethylene chloride, N,N-dimethylformamide, acetone, or the like.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process 2

The object compound [Ia] or its salt can be prepared by reacting a compound [IV] or its reactive derivative at the amino group or a salt thereof with a compound [V] or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the amino group of the compound [IV] may be a silyl derivative formed by the reaction of the compound [IV] with a silyl compound such as bis(trimethylsilyl)acetamide or mono(trimethylsilyl)acetamide, or the like.

Suitable salts of the compound [IV] and its reactive derivative can be referred to the ones as exemplified for the

compound [I].

Suitable reactive derivative at the carboxy group of the compound [V] may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like.

Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as dialkylphosphoric acid, sulfuric acid, aliphatic carboxylic acid or aromatic carboxylic acid; a symmetrical acid anhydride; an activated amide with imidazole; or an activated ester [e.g. p-nitrophenyl ester, etc.]. These reactive derivatives can optionally be selected from them according to the kind of the compound [V] to be used.

Suitable salts of the compound [V] and its reactive derivative can be referred to the ones as exemplified for the compound [I].

The reaction is usually carried out in a conventional solvent, such as methylene chloride, chloroform, pyridine, dioxane, tetrahydrofuran, N,N-dimethylformamide, or the like. In case that the compound [V] is used in the free acid form or salt form, it is preferable to carry out the reaction in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide or the like.

The reaction temperature is not critical and the reaction can be carried out under cooling, at ambient temperature, or under heating.

This reaction is preferably carried out in the presence of a conventional inorganic base or in the presence of a conventional organic base.

Process 3

The object compound [Ib] or its salt can be prepared by reacting a compound [VI] or its reactive derivative at the carboxy group or a salt thereof with a compound [VII] or its reactive derivative at the amino group or a salt thereof.

Suitable salts of the compounds [VI] and [VII] and their reactive derivatives can be referred to the ones as exemplified for the compound [I].

This reaction can be carried out in substantially the same manner as Process 2, and therefore the reaction mode and reaction condition of this reaction are to be referred to those explained in Process 2.

Process 4

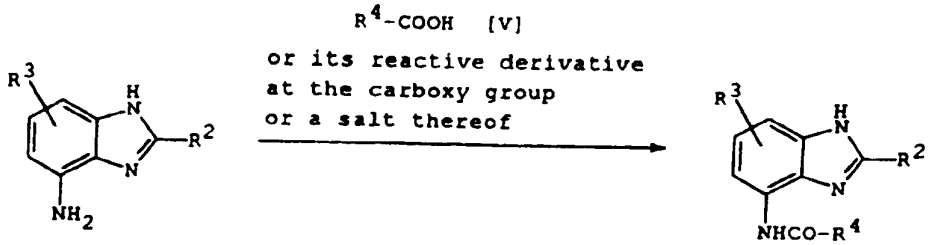
The object compound [Id] or its salt can be prepared by reacting a compound [Ic] or its reactive derivative at the carboxy group or a salt thereof with a compound [VIII] or its reactive derivative at the amino group or a salt thereof.

Suitable salts of the compound [VIII] and its reactive derivative can be referred to the ones as exemplified for the compound [I].

This reaction can be carried out in substantially the same manner as Process 2, and therefore the reaction mode and reaction condition of this reaction are to be referred to those explained in Process 2.

Some of the starting compounds in the above Processes are new, and they can be prepared by processes as illustrated in the following reaction schemes.

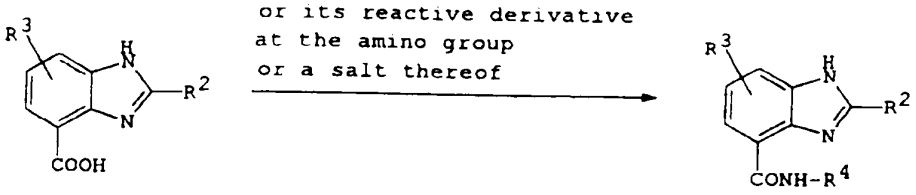
Process A



[IX]
or its reactive derivative
at the amino group or
a salt thereof

[IIa]
or its salt

Process B



[X]
or its reactive derivative
at the carboxy group
or a salt thereof

[IIb]
or its salt

wherein R^2, R^3 and R^4 are each as defined above.

Process A

The compound [IIa] or its salt can be prepared by reacting a compound [IX] or its reactive derivative at the amino group or a salt thereof with a compound [V] or its reactive derivative at the carboxy group or a salt thereof.

Suitable salts of the compound [IX] and its reactive derivative can be referred to the ones as exemplified for the compound [I].

This reaction can be carried out in substantially the same manner as Process 2, and therefore the reaction mode and reaction condition of this reaction are to be referred to those explained in Process 2.

Process B

The compound [IIb] or its salt can be prepared by reacting a compound [X] or its reactive derivative at the carboxy group or a salt thereof with a compound [VII] or its

reactive derivative at the amino group or a salt thereof.

Suitable salts of the compound [X] and its reactive derivative can be referred to the ones as exemplified for the compound [I].

This reaction can be carried out in substantially the same manner as Process 2, and therefore the reaction mode and reaction condition of this reaction are to be referred to those explained in Process 2.

The object compound [I] and the starting compounds can also be prepared by the methods of Examples mentioned below or similar manners thereto or conventional manners.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, chromatography, reprecipitation or the like.

It is to be noted that the compound [I] and the other compounds may include one or more stereoisomers and geometrical isomers due to asymmetric carbon atoms and double bonds, and all of such isomers and mixture thereof are included within the scope of this invention.

The object compound [I] and pharmaceutically acceptable salts thereof are the inhibitors of vacuolar-type (V-type) H^+-adenosine triphosphatase (ATPase), especially osteoclast H^+-ATPase, the inhibitors of bone resorption, the inhibitors of bone metastasis and useful for the prevention and/or the treatment of bone disease caused by abnormal bone metabolism such as osteoporosis (especially, postmenopausal osteoporosis); hyper-calcemia; hyperparathyroidism; Paget's bone diseases; osteolysis; hypercalcemia of malignancy with or without bone metastasis; rheumatoid arthritis; periodontitis; osteoarthritis; ostealgia; osteopenia; cancer cachexia; malignant tumor; or the like in human being or animals.

Further, it is expected that the object compound (I) and a pharmaceutically acceptable salt thereof of the present

invention are useful for the prevention and/or the treatment of tumors, especially those related to renal cancer, melanoma, colon cancer, lung cancer and leukemia; viral conditions (e.g. those involving *Semliki Forest, Vesicular Stomatitis, Newcastle Disease, Influenza A* and *B, HIV* viruses); ulcers (e.g. chronic gastritis and peptic ulcer induced by *Helicobacter pylori*); autoimmune diseases; transplantation; hypercholesterolemic and atherosclerotic diseases; AIDS; Alzheimer's disease; angiogenic diseases, such as rheumatoid arthritis, diabetic retinopathy, psoriasis and solid tumors; or the like in human being or animals, and useful for regulating male fertility in human being or animals.

In order to illustrate the usefulness of the object compound [I], the pharmacological test data of some representative compounds of the compound [I] are shown in the following.

Test (Bone organ culture) :

Test Method

Calvariae from Wistar rats were excised and cultured in wells of 12-well culture plates containing 2 ml of Dulbecco's modified minimum essential medium supplemented with 10% fetal bovine serum and 10^{-8}M human parathyroid hormone fragment (1-34) [PTH] in the presence of the test compound (dose : 1×10^{-5}M). In control dishes, PTH was not added. Control and PTH control were exposed to an equivalent concentration of the vehicle. Six days later, the concentration of calcium ([Ca]) in the medium was measured by methylxylenol blue method and the percentage of inhibition of PTH-induced bone resorption was calculated according to following formula :

$$\text{Inhibition (\%)} = \frac{C_P - C_D}{C_P - C_0} \times 100$$

C_P : [Ca] in PTH control dishes

C_D : [Ca] in the test compound dishes

C_0 : [Ca] in control dishes

As a result of this test, the compound [I] showed over 50% inhibition of PTH-induced bone resorption.

For therapeutic purpose, the compound [I] and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid, semi-solid or liquid excipient suitable for oral, parenteral such as intravenous, intramuscular, subcutaneous or intraarticular, external such as topical, enteral, intrarectal, transvaginal, inhalant, ophthalmic, nasal or hypoglossal administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, suppositories, solution, lotion, suspension, emulsion, ointment, gel, cream, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound [I] will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound [I] may be effective for preventing and/or treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

The following Examples are given for the purpose of illustrating this invention.

Example 1

(1) A mixture of 1,2-dimethyl-4-nitro-1H-benzimidazole (330 mg) and 10% palladium on carbon (40 mg) in methanol (10 ml) was stirred for 1 hour at ambient temperature under 4 atmospheric pressure of hydrogen. Insoluble material was filtered off, and the filtrate was concentrated in vacuo to give 4-amino-1,2-dimethyl-1H-benzimidazole (280 mg).

mp : 172-173°C

NMR ($CDCl_3$, δ) : 2.58 (3H, s), 3.66 (3H, s), 4.27 (2H, br s), 6.50 (1H, d, J=7Hz), 6.68 (1H, d, J=7Hz), 7.04 (1H, t, J=7Hz)

(2) A mixture of 4-amino-1,2-dimethyl-1H-benzimidazole (100 mg), 2,6-dichlorobenzoyl chloride (137 mg) and triethylamine (94 mg) in ethylene chloride (5 ml) was refluxed for 8 hours. After cooling, the mixture was diluted with methylene chloride, washed with brine, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give 4-(2,6-dichlorobenzoylamino)-1,2-dimethyl-1H-benzimidazole (125 mg).

mp : 251-252°C

NMR ($CDCl_3$, δ) : 2.57 (3H, s), 3.72 (3H, s), 7.08 (1H, d, J=7Hz), 7.20-7.40 (4H, m), 8.52 (1H, d, J=7Hz), 8.57 (1H, br s)

its hydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 2.82 (3H, s), 3.93 (3H, s), 7.50-7.64 (4H, m), 7.72 (1H, d, J=8Hz), 8.09 (1H, d, J=8Hz), 11.36 (1H, br s)

Example 2

4-(2,6-Dichlorobenzoylamino)-2-methyl-1H-benzimidazole was obtained by reacting 4-amino-2-methyl-1H-benzimidazole with 2,6-dichlorobenzoyl chloride according to a similar

manner to that of Example 1-(2).

mp : 212-213°C

Example 3

(1) A solution of 3-nitro-1,2-phenylenediamine (1.0 g) in trifluoroacetic acid (10 ml) was refluxed overnight. The reaction mixture was cooled and evaporated in vacuo. The residue was diluted with water and the solution was adjusted to pH 4 with aqueous 1N sodium hydroxide. Then, the mixture was extracted with ethyl acetate and the extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from n-hexane to give 4-nitro-2-trifluoromethyl-1H-benzimidazole (1.26 g).

mp : 145-146°C

NMR (DMSO-d_6, δ) : 7.60 (1H, t, J=7.5Hz), 8.29 (1H, d, J=7.5Hz), 8.34 (1H, d, J=7.5Hz)

(2) A mixture of 4-nitro-2-trifluoromethyl-1H-benzimidazole (1.1 g), activated carbon (100 mg) and ferric chloride hexahydrate (24 mg) in methanol (10 ml) was stirred at 60°C. To the mixture was added hydrazine hydrate (1.55 g) dropwise. The mixture was stirred at 60°C for 3 hours and filtered. The filtrate was evaporated in vacuo. The residue was treated with brine and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from a mixture of dichloromethane and n-hexane to give 4-amino-2-trifluoromethyl-1H-benzimidazole (0.86 g).

mp : 130-132°C

NMR (DMSO-d_6, δ) : 5.53 (2H, s), 6.45 (1H, d, J=7.5Hz), 6.76 (1H, d, J=7.5Hz), 7.06 (1H, t, J=7.5Hz)

(3) 4-(2,6-Dichlorobenzoylamino)-2-trifluromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 1-(2).
mp : 181-182°C

Example 4

(1) 2-Ethyl-4-nitro-1H-benzimidazole was obtained by reacting 3-nitro-1,2-phenylenediamine with propionic acid according to a similar manner to that of Example 3-(1).
NMR ($CDCl_3$, δ) : 1.52 (3H, t, J=8Hz), 3.05 (2H, q, J=8Hz), 7.34 (1H, t, J=7Hz), 8.04 (1H, d, J=7Hz), 8.12 (1H, d, J=7Hz)

(2) 4-Amino-2-ethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 3-(2).

(3) 4-(2,6-Dichlorobenzoylamino)-2-ethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 1-(2).
mp : 241-246°C
NMR (DMSO-d_6, δ) : 1.42 (3H, t, J=8Hz), 3.15 (2H, q, J=8Hz), 7.40-7.65 (7H, m), 8.13 (1H, d, J=8Hz)

Example 5

A mixture of 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (993 mg), tert-butyl bromoacetate (621 mg) and potassium carbonate (477 mg) in N,N-dimethylformamide (5 ml) was stirred at ambient temperature for 1.5 hours. The reaction mixture was poured into 0.8% hydrochloric acid and the separated oil was extracted with ethyl acetate. The extract was washed with water, aqueous saturated sodium bicarbonate solution and brine, dried over sodium sulfate and evaporated in vacuo. The residue was crystallized from a mixture of ethyl acetate and n-hexane to give 1-tert-butoxycarbonylmethyl-4-(2,6-

dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (531 mg).

mp : 166-167°C

NMR ($CDCl_3$, δ) : 1.45 (9H, s), 4.93 (2H, s), 7.14 (1H, d, J=7.5Hz), 7.30-7.45 (3H, m), 7.51 (1H, t, J=7.5Hz), 8.59 (1H, d, J=7.5Hz), 8.61 (1H, br s)

Example 6

Potassium tert-butoxide (193 mg) was added to a mixture of 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole (200 mg), 4-chloromethylpyridine hydrochloride (123 mg) and sodium carbonate (79 mg) in N,N-dimethylformamide at 4°C. The mixture was stirred at 4°C for 30 minutes and at ambient temperature for 1 hour and to the mixture was added 4-chloromethylpyridine hydrochloride (12 mg). After stirring for 1 hour at ambient temperature, the mixture was partitioned between ethyl acetate and brine. The organic layer was separated, washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was dissolved in methanolic hydrogen chloride. The solution was evaporated in vacuo and the crystalline residue was triturated with 2-propanol to give 4-(2,6-dichlorobenzoylamino)-2-methyl-1-(pyridin-4-yl)methyl-1H-benzimidazole dihydrochloride (98 mg).

mp : >250°C

NMR (DMSO-d_6, δ) : 2.80 (3H, s), 6.00 (2H, s), 7.44-7.62 (5H, m), 7.75 (2H, d, J=8Hz), 8.21 (1H, d, J=8Hz), 8.83 (2H, d, J=8Hz), 11.41 (1H, br s)

Example 7

The following compounds were obtained according to a similar manner to that of Example 5 or 6.

(1) 1-(2-Acetoxyethyl)-4-(2,6-dichlorobenzoylamino)-2-

methyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole and 2-acetoxyethyl bromide)
mp : 177-178°C
NMR ($CDCl_3$, δ) : 2.00 (3H, s), 2.61 (3H, s), 4.38 (4H, s), 7.11 (1H, d, J=7Hz), 7.25-7.40 (4H, m), 8.44 (1H, d, J=7Hz), 8.59 (1H, br s)

(2) 4-(2,6-Dichlorobenzoylamino)-2-methyl-1-(pyridin-3-yl)methyl-1H-benzimidazole dihydrochloride
(from 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole and 3-chloromethylpyridine hydrochloride)
mp : >250°C
NMR (DMSO-d_6, δ) : 2.88 (3H, s), 5.88 (2H, s), 7.45-7.65 (5H, m), 7.82 (1H, dd, J=5Hz, 7Hz), 8.70-8.80 (2H, m), 8.79 (1H, d, J=5Hz), 8.92 (1H, s)

(3) 4-(2,6-Dichlorobenzoylamino)-2-methyl-1-(2-oxopropyl)-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole and 2-oxopropyl chloride)
mp : 222-224°C
NMR ($CDCl_3$, δ) : 2.23 (3H, s), 2.47 (3H, s), 4.83 (2H, s), 6.92 (1H, d, J=7Hz), 7.25-7.40 (4H, m), 8.44 (1H, d, J=7Hz), 8.55 (1H, br s)

its hydrochloride
mp : >250°C
NMR (DMSO-d_6, δ) : 2.37 (3H, s), 2.70 (3H, s), 5.61 (2H, s), 7.45-7.70 (5H, m), 8.09 (1H, d, J=7Hz)

(4) 4-(2,6-Dichlorobenzoylamino)-1-(pyridin-3-yl)carbonylmethyl-2-trifluoromethyl-1H-benzimidazole hydrochloride
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-

benzimidazole and pyridin-3-ylcarbonylmethyl bromide hydrobromide)
mp : 240-242°C
NMR (DMSO-d_6, δ) : 6.37 (2H, s), 7.45-7.58 (4H, m), 7.62 (1H, d, J=7Hz), 7.77 (1H, dd, J=5Hz, 7Hz), 8.25 (1H, d, J=7Hz), 8.56 (1H, d, J=7Hz), 8.98 (1H, d, J=5Hz), 9.40 (1H, s)

(5) 1-tert-Butoxycarbonylmethyl-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole and tert-butyl bromoacetate)
mp : 194-195°C
NMR ($CDCl_3$, δ) : 1.47 (9H, s), 2.55 (3H, s), 4.72 (2H, s), 7.03 (1H, d, J=7.5Hz), 7.30-7.40 (4H, m), 8.45 (1H, d, J=7.5Hz), 8.60 (1H, br s)

(6) 4-(2,6-Dichlorobenzoylamino)-2-methyl-1-allyl-1H-benzimidazole hydrochloride
(from 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole and allyl bromide)
mp : 248-250°C
NMR ($CDCl_3$, δ) : 2.82 (3H, s), 4.89 (2H, d, J=5Hz), 5.08 (1H, d, J=16Hz), 5.40 (1H, d, J=10Hz), 5.95 (1H, m), 7.20 (1H, d, J=8Hz), 7.27-7.42 (3H, m), 7.50 (1H, t, J=8Hz), 8.78 (1H, d, J=8Hz)

(7) 4-(2,6-Dichlorobenzoylamino)-1-(3,3-diethoxypropyl)-2-methyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole and 3,3-diethoxypropyl chloride)
mp : 130-132°C
NMR ($CDCl_3$, δ) : 1.22 (6H, t, J=7Hz), 2.10 (2H, q, J=7Hz), 2.59 (3H, s), 3.40-3.51 (2H, m), 3.59-3.70 (2H, m), 4.23 (2H, t, J=7Hz), 4.46 (1H, t, J=5Hz),

7.14 (1H, d, J=8Hz), 7.26-7.39 (4H, m), 8.43 (1H, d, J=8Hz), 8.57 (1H, s)

(8) 4-(2,6-Dichlorobenzoylamino)-1-ethyl-2-methyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole and ethyl iodide)
mp : 244-246°C
NMR ($CDCl_3$, δ) : 1.42 (3H, t, J=7Hz), 2.59 (3H, s), 4.17 (2H, q, J=7Hz), 7.11 (1H, d, J=8Hz), 7.27-7.40 (4H, m), 8.43 (1H, d, J=8Hz), 8.57 (1H, s)

(9) 1-(3-Chloropropyl)-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole and 1-bromo-3-chloropropane)
NMR ($CDCl_3$, δ) : 2.23-2.35 (2H, m), 2.67 (3H, s), 3.55 (2H, t, J=7Hz), 4.32 (2H, t, J=7Hz), 7.15 (1H, d, J=8Hz), 7.27-7.39 (4H, m), 8.44 (1H, d, J=8Hz), 8.60 (1H, s)

(10) 4-(2,6-Dichlorobenzoylamino)-1-(pyridin-2-yl)methyl-2-trifluoromethyl-1H-benzimidazole hydrochloride
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-chloromethylpyridine hydrochloride)
mp : 222-224°C
NMR (DMSO-d_6, δ) : 5.85 (2H, s), 7.30-7.38 (2H, m), 7.40-7.60 (5H, m), 7.86 (1H, dt, J=8Hz, 2Hz), 8.22 (1H, d, J=8Hz), 8.45 (1H, d, J=8Hz)

(11) 4-(2,6-Dichlorobenzoylamino)-1-(1-ethoxycarbonylethyl)-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and ethyl 2-bromopropionate)
NMR ($CDCl_3$, δ) : 1.18 (3H, t, J=7Hz), 1.37 (3H, d,

J=7Hz), 4.23 (2H, q, J=7Hz), 5.36 (1H, q, J=7Hz), 7.16 (1H, d, J=8Hz), 7.31-7.49 (4H, m), 8.57 (1H, d, J=8Hz), 8.62 (1H, s)

(12) 4-(2,6-Dichlorobenzoylamino)-2-ethyl-1-(2-oxopropyl)-1H-benzimidazole hydrochloride
(from 4-(2,6-dichlorobenzoylamino)-2-ethyl-1H-benzimidazole and 2-oxopropyl chloride)
mp : 246-258°C
NMR (DMSO-d_6, δ) : 1.34 (3H, t, J=7Hz), 2.37 (3H, s), 3.05 (2H, q, J=7Hz), 5.63 (2H, s), 7.39-7.64 (6H, m), 8.28 (1H, d, J=8Hz)

(13) 4-(2,6-Dichlorobenzoylamino)-2-ethyl-1-methyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-ethyl-1H-benzimidazole and methyl iodide)
mp : 244-247°C
NMR ($CDCl_3$, δ) : 1.38 (3H, t, J=7Hz), 2.90 (2H, q, J=7Hz), 3.73 (3H, s), 7.10 (1H, d, J=8Hz), 7.27-7.39 (4H, m), 8.44 (1H, d, J=8Hz), 8.65 (1H, s)

(14) 4-(2,6-Dichlorobenzoylamino)-1-(pyridin-4-yl)carbonylmethyl-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and pyridin-4-ylcarbonylmethyl bromide hydrobromide)
mp : 179-180°C
NMR (DMSO-d_6, δ) : 6.32 (2H, s), 7.40-7.70 (5H, m), 8.03 (2H, dd, J=1Hz, 7.5Hz), 8.25 (1H, d, J=7.5Hz), 8.94 (2H, dd, J=1Hz, 7.5Hz), 11.20 (1H, s)

its hydrochloride
mp : 235-246°C
NMR (DMSO-d_6, δ) : 6.32 (2H, s), 7.40-7.70 (5H, m),

8.09 (2H, d, J=7.5Hz), 8.24 (1H, d, J=7.5Hz), 8.95 (2H, d, J=7.5Hz), 11.20 (1H, s)

(15) 1-Benzyl-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole and benzyl bromide)
mp : 204-205°C
NMR (DMSO-d_6, δ) : 3.32 (3H, s), 5.48 (2H, s), 7.10-7.20 (3H, m), 7.20-7.40 (4H, m), 7.40-7.60 (3H, m), 8.04 (1H, d, J=7.5Hz), 10.79 (1H, s)

its hydrochloride
mp : 242-252°C
NMR (DMSO-d_6, δ) : 2.83 (3H, s), 5.70 (2H, s), 7.20-7.70 (10H, m), 8.10 (1H, d, J=7.5Hz), 11.28 (1H, s)

(16) 1-Benzoylmethyl-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole and benzoylmethyl bromide)
mp : 228-229°C
NMR (DMSO-d_6, δ) : 2.43 (3H, s), 6.03 (2H, s), 7.14 (1H, t, J=7.5Hz), 7.26 (1H, d, J=7.5Hz), 7.40-7.60 (3H, m), 7.64 (2H, t, J=7.5Hz), 7.77 (1H, t, J=7.5Hz), 8.03 (1H, d, J=7.5Hz), 8.15 (2H, d, J=7.5Hz)

its hydrochloride
mp : 289-298°C
NMR (DMSO-d_6, δ) : 2.76 (3H, s), 6.33 (2H, s), 7.50 (1H, t, J=7.5Hz), 7.50-7.70 (6H, m), 7.80 (1H, t, J=7.5Hz), 8.04 (1H, d, J=7.5Hz), 8.16 (2H, d, J=7.5Hz), 11.25 (1H, br s)

(17) 4-(2,6-Dichlorobenzoylamino)-1-(2-methoxyethyl)-2-methyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole and 2-methoxyethyl bromide)
mp : 155-156°C
NMR ($CDCl_3$, δ) : 2.60 (3H, s), 3.28 (3H, s), 3.69 (2H, t, J=5Hz), 4.28 (2H, t, J=5Hz), 7.10 (1H, d, J=7.5Hz), 7.25-7.40 (4H, m), 8.43 (1H, d, J=7.5Hz), 8.62 (1H, br s)

its hydrochloride
mp : 196-206°C
NMR (DMSO-d_6, δ) : 2.83 (3H, s), 3.22 (3H, s), 3.73 (2H, m), 4.62 (2H, m), 7.40-7.70 (4H, m), 7.71 (1H, d, J=8Hz), 8.03 (1H, d, J=8Hz), 11.23 (1H, s)

(18) 1-(2-Cyanoethyl)-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole and 2-cyanoethyl bromide)
mp : 221.5-222.5°C
NMR (DMSO-d_6, δ) : 2.61 (3H, s), 3.06 (2H, t, J=7Hz), 4.54 (2H, t, J=7Hz), 7.21 (1H, t, J=8Hz), 7.30-7.60 (4H, m), 8.05 (1H, d, J=8Hz), 10.77 (1H, s)

its hydrochloride
mp : 220-245°C
NMR (DMSO-d_6, δ) : 2.75 (3H, s), 3.11 (2H, t, J=7Hz), 4.67 (2H, t, J=7Hz), 7.40 (1H, br t, J=8Hz), 7.40-7.60 (3H, m), 7.64 (1H, br d, J=8Hz), 8.03 (1H, d, J=8Hz), 11.03 (1H, br s)

(19) 4-(2,6-Dichlorobenzoylamino)-1-(2-oxopropyl)-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-

benzimidazole and 2-oxopropyl chloride)
mp : 228-229°C
NMR ($CDCl_3$, δ) : 2.30 (3H, s), 5.09 (2H, s), 7.03 (1H, d, J=8Hz), 7.30-7.45 (3H, m), 7.50 (1H, t, J=8Hz), 8.59 (1H, d, J=8Hz), 8.60 (1H, s)

(20) 4-(2,6-Dichlorobenzoylamino)-1-methyl-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and methyl iodide)
mp : 215-216°C
NMR ($CDCl_3$, δ) : 3.97 (3H, s), 7.24 (1H, d, J=7.5Hz), 7.30-7.50 (3H, m), 7.51 (1H, t, J=7.5Hz), 8.58 (1H, d, J=7.5Hz), 8.63 (1H, br s)

(21) 4-(2,6-Dichlorobenzoylamino)-1-(pyridin-3-yl)methyl-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 3-chloromethylpyridine hydrochloride)
mp : 236-237°C
NMR (DMSO-d_6, δ) : 5.79 (2H, s), 7.35 (1H, dd, J=2Hz, 8Hz), 7.40-7.60 (6H, m), 8.26 (1H, d, J=8Hz), 8.40-8.60 (2H, m), 11.21 (1H, s)

its hydrochloride
mp : >250°C
NMR (DMSO-d_6, δ) : 5.89 (2H, s), 7.40-7.60 (5H, m), 7.71 (1H, dd, J=6Hz, 8Hz), 7.88 (1H, d, J=8Hz), 8.28 (1H, d, J=8Hz), 8.70-8.80 (2H, m), 11.23 (1H, s)

(22) 4-(2,6-Dichlorobenzoylamino)-1-(2-morpholinoethyl)-2-trifluromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-morpholinoethyl chloride

hydrochloride)
mp : 194-195°C
NMR (DMSO-d_6, δ) : 2.40-2.50 (4H, m), 2.70 (2H, t, J=7Hz), 3.50-3.60 (4H, m), 4.51 (2H, t, J=7Hz), 7.40-7.70 (5H, m), 8.22 (1H, d, J=8Hz), 11.12 (1H, s)

its hydrochloride
mp : 226-236°C
NMR (DMSO-d_6, δ) : 3.10-4.10 (11H, m), 4.8-5.0 (1H, br), 7.40-7.60 (4H, m), 7.78 (1H, br), 8.26 (1H, d, J=8Hz), 11.19 (1H, s)

(23) 4-(2,6-Dichlorobenzoylamino)-1-(pyridin-4-yl)methyl-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 4-chloromethylpyridine hydrochloride)
mp : 187-188°C
NMR (DMSO-d_6, δ) : 5.80 (2H, s), 7.07 (2H, d, J=8Hz), 7.40-7.70 (5H, m), 8.28 (1H, m), 8.52 (2H, d, J=8Hz), 11.24 (1H, s)

its hydrochloride
mp : 225-237°C
NMR (DMSO-d_6, δ) : 6.01 (2H, s), 7.40-7.70 (7H, m), 8.30 (1H, dd, J=2Hz, 7Hz), 8.74 (2H, d, J=7Hz), 11.27 (1H, s)

(24) 1-(2-Acetoxyethyl)-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-acetoxyethyl bromide)
mp : 161-162°C
NMR ($CDCl_3$, δ) : 4.47 (2H, t, J=6Hz), 4.60 (2H, t, J=6Hz), 7.20-7.50 (4H, m), 7.51 (1H, t, J=8Hz),

8.58 (1H, d, J=8Hz), 8.62 (1H, s)

(25) 1-[(5-Chlorothiophen-2-yl)carbonylmethyl]-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and (5-chlorothiophen-2-yl)carbonylmethyl bromide)
mp : 216-217°C
NMR (DMSO-d_6, δ) : 6.18 (2H, s), 7.40-7.70 (6H, m), 8.24 (1H, d, J=8Hz), 8.30 (1H, d, J=2Hz), 11.20 (1H, s)

(26) 4-(2,6-Dichlorobenzoylamino)-1-isopropyl-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and isopropyl iodide)
mp : 182-183°C
NMR ($CDCl_3$, δ) : 1.72 (6H, d, J=7Hz), 4.93 (1H, m), 7.30-7.50 (5H, m), 8.55 (1H, d, J=8Hz), 8.67 (1H, s)

(27) 4-(2,6-Dichlorobenzoylamino)-1-[2-chloro-4,5-(methylenedioxy)benzyl]-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-chloro-4,5-(methylenedioxy)benzyl chloride)
mp : 200-201°C
NMR ($CDCl_3$, δ) : 5.53 (2H, s), 5.93 (2H, s), 5.98 (1H, s), 6.92 (1H, s), 7.03 (1H, d, J=8Hz), 7.30-7.50 (4H, m), 8.59 (1H, d, J=8Hz), 8.65 (1H, s)

(28) 4-(2,6-Dichlorobenzoylamino)-1-[2-(pyrrolidin-1-yl)ethyl]-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-

benzimidazole and 2-(pyrrolidin-1-yl)ethyl chloride hydrochloride)

NMR (DMSO-d_6, δ) : 1.60-1.80 (4H, m), 2.40-2.60 (4H, m), 2.84 (2H, m), 4.51 (2H, m), 7.40-7.60 (5H, m), 8.22 (1H, d, J=8Hz), 11.12 (1H, s)

its hydrochloride

mp : 238-242°C

NMR (DMSO-d_6, δ) : 1.8-2.2 (4H, m), 3.0-3.2 (2H, m), 3.6-3.8 (4H, m), 4.85 (2H, m), 7.4-7.6 (4H, m), 7.78 (1H, d, J=8Hz), 8.27 (1H, d, J=8Hz), 11.19 (1H, s)

(29) 1-Cyanomethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and cyanomethyl bromide)

mp : 211-213°C

NMR (DMSO-d_6, δ) : 5.84 (2H, s), 7.40-7.60 (3H, m), 7.63 (1H, d, J=8Hz), 7.74 (1H, d, J=8Hz), 8.29 (1H, d, J=8Hz), 11.25 (1H, s)

(30) 4-(2,6-Dichlorobenzoylamino)-1-(2-phthalimidoethyl)-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-phthalimidoethyl bromide)

NMR ($CDCl_3$, δ) : 4.16 (2H, t, J=7Hz), 4.60 (2H, t, J=7Hz), 7.20-7.40 (5H, m), 7.70-7.90 (4H, m), 8.49 (1H, d, J=8Hz), 8.57 (1H, s)

(31) 4-(2,6-Dichlorobenzoylamino)-1-(pyridin-3-yl)carbonylmethyl-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and pyridin-3-ylcarbonylmethyl bromide hydrobromide)

mp : 199-200°C

NMR (DMSO-d_6, δ) : 6.35 (2H, s), 7.40-7.65 (5H, m), 7.69 (1H, dd, J=5Hz, 8Hz), 8.25 (1H, d, J=8Hz), 8.48 (1H, d, J=8Hz), 8.93 (1H, d, J=5Hz), 9.37 (1H, s)

(32) 1-(3-Cyanobenzyl)-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 3-cyanobenzyl bromide)
mp : 225-227°C
NMR (DMSO-d_6, δ) : 5.79 (2H, s), 7.34 (1H, d, J=8Hz), 7.4-7.6 (6H, m), 7.70-7.90 (2H, m), 8.27 (1H, m)

(33) 1-Cyanomethyl-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole and cyanomethyl chloride)
mp : 240-242°C
NMR ($CDCl_3$-CD_3OD, δ) : 2.63 (3H, s), 5.03 (2H, s), 7.14 (1H, d, J=8Hz), 7.28-7.40 (4H, m), 8.50 (1H, d, J=8Hz)

(34) 4-(2,6-Dichlorobenzoylamino)-2-methyl-1-(pyridin-2-yl)methyl-1H-benzimidazole dihydrochloride
(from 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole and 2-chloromethylpyridine hydrochloride)
mp : >250°C
NMR (DMSO-d_6, δ) : 2.88 (3H, s), 5.85 (2H, s), 7.35 (1H, m), 7.45-7.64 (6H, m), 7.88 (1H, t, J=8Hz), 8.08 (1H, d, J=8Hz), 8.46 (1H, m), 11.31 (1H, br s)

(35) 4-(2,6-Dichlorobenzoylamino)-2-methyl-1-(4-nitrobenzyl)-1H-benzimidazole hydrochloride
(from 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-

benzimidazole and 4-nitrobenzyl bromide)
mp : >250°C
NMR (DMSO-d_6, δ) : 2.80 (3H, s), 5.88 (2H, s), 7.42-7.62 (7H, m), 8.10 (1H, d, J=8Hz), 8.21 (2H, d, J=8Hz), 11.28 (1H, br s)

(36) 4-(2,6-Dichlorobenzoylamino)-1-(2,3-epoxypropyl)-2-methyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole and 2,3-epoxypropyl bromide)
mp : 198-200°C
NMR ($CDCl_3$, δ) : 2.46 (1H, m), 2.60 (3H, s), 2.83 (1H, t, J=5Hz), 3.30 (1H, m), 4.18 (1H, dd, J=6Hz, 15Hz), 4.52 (1H, dd, J=2Hz, 15Hz), 7.13 (1H, d, J=8Hz), 7.24-7.40 (4H, m), 8.44 (1H, d, J=8Hz), 8.54 (1H, br s)

(37) 4-(2,6-Dichlorobenzoylamino)-1-(2-furylmethyl)-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-furylmethyl chloride)
mp : 119-121°C
NMR (DMSO-d_6, δ) : 5.70 (2H, s), 6.44 (1H, s), 6.62 (1H, s), 7.40-7.55 (4H, m), 7.60 (1H, s), 7.68 (1H, d, J=8Hz), 8.22 (1H, d, J=8Hz)

Example 8

A mixture of 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (187 mg), 1-bromo-3-chloropropane (95 mg) and potassium carbonate (104 mg) in N,N-dimethylformamide (3 ml) was stirred at ambient temperature overnight. The mixture was poured into a mixture of ice and water. The separated oil was extracted with ethyl acetate and the extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was

purified by column chromatography on silica gel. The obtained oil was dissolved in N,N-dimethylformamide (2 ml) and to the solution was added 1-methylpiperazine (100 mg). The solution was stirred at 50°C overnight and poured into water. The mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil containing 4-(2,6-dichlorobenzoylamino)-1-[3-(4-methylpiperazin-1-yl)propyl]-2-trifluoromethyl-1H-benzimidazole was dissolved in 10% methanolic hydrogen chloride. The solution was evaporated in vacuo and the residue was crystallized from ethyl acetate to give 4-(2,6-dichlorobenzoylamino)-1-[3-(4-methylpiperazin-1-yl)propyl]-2-trifluoromethyl-1H-benzimidazole dihydrochloride (98 mg).

mp : >250°C

NMR (DMSO-d_6, δ) : 2.25 (2H, m), 2.90 (3H, s), 3.20-3.70 (10H, m), 4.51 (2H, t, J=7Hz), 7.45-7.55 (4H, m), 7.69 (1H, d, J=7Hz), 8.23 (1H, d, J=7Hz)

Example 9

A solution of 1-tert-butoxycarbonylmethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (715 mg) in trifluoroacetic acid (5 ml) was stirred at ambient temperature for 3 hours. The mixture was evaporated in vacuo and the residue was crystallized from diethyl ether to give 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (636 mg).

mp : >250°C

NMR ($CDCl_3$:CD_3OD = 20:1, δ) : 5.03 (2H, s), 7.17 (1H, d, J=8Hz), 7.30-7.50 (3H, m), 7.52 (1H, t, J=8Hz), 8.62 (1H, d, J=8Hz)

Example 10

The following compounds were obtained according to a

similar manner to that of Example 9.

(1) 1-Carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole trifluoroacetate
mp : >250°C
NMR (DMSO-d_6, δ) : 2.66 (3H, s), 5.26 (2H, s), 7.37 (1H, t, J=8Hz), 7.40-7.70 (4H, m), 7.94 (1H, d, J=8Hz), 10.95 (1H, s)

(2) 1-Carboxymethyl-4-(2,6-dimethylbenzoylamino)-2-trifluoromethyl-1H-benzimidazole
mp : 158-164°C
NMR (DMSO-d_6, δ) : 2.33 (6H, s), 5.30 (2H, s), 7.11 (2H, d, J=8Hz), 7.24 (1H, t, J=8Hz), 7.49 (1H, t, J=8Hz), 7.63 (1H, d, J=8Hz), 7.99 (1H, d, J=8Hz)

Example 11

To a solution of 4-(2,6-dichlorobenzoylamino)-1-(1-ethoxycarbonylethyl)-2-trifluoromethyl-1H-benzimidazole (140 mg) in tetrahydrofuran (15 ml) were added 1N sodium hydroxide solution (0.44 ml) and methanol (0.5 ml), and the mixture was stirred for 1 hour at ambient temperature. The mixture was concentrated in vacuo and the residue was acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was dried and concentrated in vacuo to give 1-(1-carboxyethyl)-4-(2,6-dicholorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (131 mg).

NMR ($CDCl_3$, δ) : 1.87 (3H, d, J=7Hz), 5.38 (1H, q, J=7Hz), 7.17 (1H, d, J=8Hz), 7.25-7.36 (3H, m), 7.46 (1H, t, J=8Hz), 8.57 (1H, d, J=8Hz), 8.90 (1H, s)

Example 12

Oxalyl chloride (48 µl) was added to a suspension of 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-

1H-benzimidazole (135 mg) in dichloromethane. Then, to a mixture was added N,N-dimethylformamide (1 drop). The mixture was stirred at ambient temperature for 2 hours and evaporated in vacuo. The residue was dissolved in dioxane (1 ml) and to the solution was added 28% aqueous ammonia (5 ml) in one portion with well stirring. The mixture was extracted with ethyl acetate and the extract was washed with water, dried over sodium sulfate and evaporated in vacuo. The crystalline residue was recrystallized from a mixture of ethyl acetate and n-hexane to give 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (93 mg).

mp : >250°C

NMR (DMSO-d_6, δ) : 5.09 (2H, s), 7.40-7.60 (6H, m), 7.81 (1H, br s), 8.22 (1H, dd, J=1Hz, 7.5Hz), 11.14 (1H, s)

Example 13

Oxalyl chloride (40 µl) was added to a suspension of 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (150 mg) in dichloromethane. Then, to a mixture was added N,N-dimethylformamide (1 drop). The mixture was stirred at ambient temperature for 1 hour and evaporated in vacuo. The residue was dissolved in dichloromethane (2 ml) and 1-methylpiperazine (61 mg) was added to the solution. The solution was stirred for 30 minutes at ambient temperature, washed with water and brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diethyl ether to give 4-(2,6-dichlorobenzoylamino)-1-(4-methylpiperazin-1-yl)carbonylmethyl-2-trifluoromethyl-1H-benzimidazole (141 mg).

mp : >250°C

NMR (DMSO-d_6, δ) : 2.23 (3H, s), 2.25-2.35 (2H, m),

2.40-2.50 (2H, m), 3.40-3.50 (2H, m), 3.55-3.65 (2H, m), 5.49 (2H, s), 7.40-7.70 (5H, m), 8.24 (1H, d, J=8Hz), 11.14 (1H, s)

its hydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 2.4-3.9 (11H, m), 5.54 (2H, s), 7.40-7.60 (5H, m), 8.22 (1H, d, J=8Hz), 11.15 (1H, s)

Example 14

To a solution of 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole trifluoroacetate (150 mg) and N-methylmorpholine (37 mg) in N,N-dimethylformamide were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (70 mg) and 1-hydroxybenzotriazole (50 mg), and the mixture was stirred for 1 hour. To the mixture was added 4-aminopyridine (37 mg), and the mixture was stirred for 2 hours. The mixture was partitioned between ethyl acetate and water, and the organic layer was washed with water and brine, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1% methanol-dichloromethane) to give 4-(2,6-dichlorobenzoylamino)-2-methyl-1-[N-(pyridin-4-yl)carbamoyl]-methyl-1H-benzimidazole (60 mg).

mp : 226-228°C

NMR ($CDCl_3$, δ) : 2.57 (3H, s), 4.90 (2H, s), 7.05 (1H, d, J=8Hz), 7.25-7.45 (6H, m), 7.57 (2H, dd, J=2Hz, 8Hz), 8.38-8.45 (3H, m)

Example 15

The following compounds were obtained according to a similar manner to that of Examples 12, 13 or 14.

(1) 4-(2,6-Dichlorobenzoylamino)-2-methyl-1-

(morpholinocarbamoyl)methyl-1H-benzimidazole dihydrochloride
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole trifluoroacetate and 4-aminomorpholine)
mp : >250°C
NMR ($CDCl_3$, δ) : 2.72-3.20 (7H, m), 3.70-4.05 (4H, m), 5.18 (4/3H, s), 5.33 (2/3H, s), 7.22-7.60 (5H, m), 8.05 (2/3H, d, J=7Hz), 8.52 (1/3H, d, J=7Hz)

(2) 4-(2,6-Dichlorobenzoylamino)-1-[N-(2-hydroxyethyl)carbamoyl]methyl-2-methyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole trifluoroacetate and (2-hydroxyethyl)amine)
mp : >250°C
NMR ($CDCl_3$, δ) : 2.56 (3H, s), 3.34-3.40 (3H, m), 3.61 (2H, t, J=5Hz), 4.78 (2H, s), 7.10 (1H, d, J=8Hz), 7.28-7.43 (4H, m), 8.42 (1H, d, J=8Hz)

(3) 1-[N,N-Bis(2-methoxyethyl)carbamoyl]methyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and bis(2-methoxyethyl)amine
mp : 121-129°C
NMR ($CDCl_3$, δ) : 3.33 (3H, s), 3.48 (3H, s), 3.50-3.60 (4H, m), 3.60-3.72 (4H, m), 5.35 (2H, s), 7.11 (1H, d, J=8Hz), 7.29-7.50 (4H, m), 8.55 (1H, d, J=8Hz), 8.67 (1H, s)

(4) 1-(4-Acetylpiperazin-1-yl)carbonylmethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 1-acetylpiperazine)

mp : 160-188°C
NMR ($CDCl_3$, δ) : 2.15 (3H, s), 3.48-3.82 (8H, m), 5.14 (2H, s), 7.06 (1H, d, J=8Hz), 7.30-7.49 (4H, m), 8.57 (1H, d, J=8Hz)

(5) 4-(2,6-Dichlorobenzoylamino)-1-(4-phenylpiperazin-1-yl)carbonylmethyl-2-trifluoromethyl-1H-benzimidazole hydrochloride
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 1-phenylpiperazine)
mp : 120-180°C
NMR (DMSO-d_6, δ) : 3.15-3.26 (2H, m), 3.30-3.40 (2H, m), 3.61-3.71 (2H, m), 3.80-3.89 (2H, m), 5.57 (2H, s), 6.95 (1H, t, J=8Hz), 7.15 (2H, d, J=8Hz), 7.31 (2H, t, J=8Hz), 7.44-7.60 (6H, m), 8.22 (1H, d, J=8Hz)

(6) 4-(2,6-Dichlorobenzoylamino)-1-[N-(pyridin-4-yl)carbamoyl]methyl-2-trifluoromethyl-1H-benzimidazole hydrochloride
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluromethyl-1H-benzimidazole and 4-aminopyridine)
mp : >250°C
NMR (DMSO-d_6, δ) : 5.57 (2H, s), 7.45-7.68 (5H, m), 8.04 (2H, d, J=8Hz), 8.25 (1H, d, J=8Hz), 8.73 (2H, d, J=8Hz)

(7) 4-(2,6-Dichlorobenzoylamino)-1-[N-(pyridin-4-ylmethyl)carbamoyl]methyl-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 4-aminomethylpyridine)
mp : >250°C
NMR ($CDCl_3$, δ) : 4.41 (2H, s), 5.05 (2H, s), 7.16-7.23

(3H, m), 7.34-7.45 (3H, m), 7.51 (1H, t, J=8Hz), 8.45 (2H, d, J=8Hz), 8.55 (1H, d, J=8Hz)

its hydrochloride
mp : 248-257°C
NMR (DMSO-d_6, δ) : 4.61 (2H, d, J=6Hz), 5.35 (2H, s), 7.45-7.60 (5H, m), 7.87 (2H, d, J=8Hz), 8.22 (1H, d, J=8Hz), 8.86 (2H, d, J=8Hz), 9.33 (1H, t, J=7Hz)

(8) 4-(2,6-Dichlorobenzoylamino)-1-[N-(4-dimethylaminophenyl)carbamoyl]methyl-2-trifluoromethyl-1H-benzimidazole hydrochloride
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and N,N-dimethyl-1,4-phenylenediamine)
mp : >250°C
NMR (DMSO-d_6, δ) : 3.04 (6H, s), 5.40 (2H, s), 7.30-7.75 (9H, m), 8.25 (1H, d, J=8Hz)

(9) 4-(2,6-Dichlorobenzoylamino)-1-[N-methyl-N-(pyridin-2-yl)carbamoyl]methyl-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-methylaminopyridine)
mp : 194-196°C
NMR ($CDCl_3$, δ) : 3.45 (3H, s), 5.30 (2H, s), 7.17 (1H, d, J=8Hz), 7.28-7.42 (5H, m), 7.48 (1H, t, J=8Hz), 7.89 (1H, dt, J=8Hz, 2Hz), 8.53-8.65 (3H, m)

(10) 4-(2,6-Dichlorobenzoylamino)-1-[N-(2-methoxyethyl)carbamoyl]methyl-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and (2-methoxyethyl)amine)

mp : 217-220°C

NMR ($CDCl_3$, δ) : 3.25 (3H, s), 3.35-3.49 (4H, m), 4.97 (2H, s), 5.87-5.95 (1H, br), 7.19 (1H, d, J=8Hz), 7.31-7.42 (3H, m), 7.53 (1H, t, J=8Hz), 8.61 (1H, d, J=8Hz), 8.66 (1H, s)

(11) 1-[N-(Cyanomethyl)carbamoyl]methyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and (cyanomethyl)amine)
mp : 238-243°C
NMR ($CDCl_3$, δ) : 4.12 (2H, s), 5.00 (2H, s), 7.15 (1H, d, J=8Hz), 7.30-7.45 (3H, m), 7.51 (1H, t, J=8Hz), 8.56 (1H, d, J=8Hz)

(12) 4-(2,6-Dichlorobenzoylamino)-2-trifluoromethyl-1-[N-(3-trifluoromethylphenyl)carbamoyl]methyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 3-trifluoromethylaniline)
mp : 120-124°C
NMR ($CDCl_3$, δ) : 5.10 (2H, s), 7.18 (1H, d, J=8Hz), 7.32-7.47 (5H, m), 7.51 (1H, t, J=8Hz), 7.58-7.63 (1H, m), 7.74 (2H, s), 8.58 (1H, d, J=8Hz), 8.67 (1H, s)

(13) 4-(2,6-Dichlorobenzoylamino)-1-[N-(2,2,2-trifluoroethyl)carbamoyl]methyl-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluromethyl-1H-benzimidazole and (2,2,2-trifluoroethyl)amine)
mp : >250°C
NMR ($CDCl_3$, δ) : 3.89 (2H, q, J=8Hz), 5.02 (2H, s), 7.17 (1H, d, J=8Hz), 7.31-7.46 (3H, m), 7.52 (1H,

t, J=8Hz), 8.59 (1H, d, J=8Hz)

(14) 4-(2,6-Dichlorobenzoylamino)-1-[N-(thiazol-2-yl)carbamoyl]methyl-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-aminothiazole)
mp : >250°C
NMR ($CDCl_3$, δ) : 5.25 (2H, s), 7.03 (1H, d, J=4Hz), 7.19 (1H, d, J=8Hz), 7.31-7.45 (4H, m), 7.52 (1H, t, J=8Hz), 8.62 (1H, d, J=8Hz)

(15) 4-(2,6-Dichlorobenzoylamino)-1-[1-(morpholinocarbonyl)-ethyl]-2-trifluoromethyl-1H-benzimidazole
(from 1-(1-carboxyethyl)-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and morpholine)
mp : >250°C
NMR ($CDCl_3$, δ) : 1.80 (3H, d, J=7Hz), 3.00-3.73 (8H, m), 5.50 (1H, q, J=7Hz), 7.32-7.50 (5H, m), 8.57 (1H, d, J=8Hz), 8.60 (1H, s)

(16) 1-Carbamoylmethyl-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole trifluoroacetate and 28% aqueous ammonia)
mp : >250°C
NMR (DMSO-d_6, δ) : 2.48 (3H, s), 4.84 (2H, s), 7.10-7.30 (2H, m), 7.37 (1H, br s), 7.40-7.60 (3H, m), 7.75 (1H, br s), 8.04 (1H, d, J=7.5Hz), 10.75 (1H, br s)

its hydrochloride
mp : 182-193°C
NMR (DMSO-d_6, δ) : 2.75 (3H, s), 5.10 (2H, s), 7.40-7.70 (6H, m), 7.90-8.10 (2H, m), 11.16 (1H, br s)

(17) 4-(2,6-Dichlorobenzoylamino)-1-(N,N-dimethylcarbamoyl)methyl-2-methyl-1H-benzimidazole (from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole trifluoroacetate and dimethylamine)
mp : 218-219°C
NMR (DMSO-d_6, δ) : 2.40 (3H, s), 2.87 (3H, s), 3.15 (3H, s), 5.20 (2H, s), 7.15 (1H, t, J=7.5Hz), 7.24 (1H, d, J=7.5Hz), 7.40-7.60 (3H, m), 8.01 (1H, d, J=7.5Hz), 10.72 (1H, s)

its hydrochloride
mp : 275-284°C
NMR (DMSO-d_6, δ) : 2.65 (3H, s), 2.90 (3H, s), 3.17 (3H, s), 5.45 (2H, s), 7.44 (1H, br t, J=7.5Hz), 7.50-7.70 (4H, m), 8.00 (1H, d, J=7.5Hz), 11.10 (1H, br s)

(18) 4-(2,6-Dichlorobenzoylamino)-1-[N-(pyridin-3-yl)carbamoyl]methyl-2-trifluoromethyl-1H-benzimidazole (from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 3-aminopyridine)
NMR (DMSO-d_6, δ) : 5.40 (2H, s), 7.37 (1H, dd, J=6Hz, 8Hz), 7.40-7.50 (5H, m), 8.01 (1H, dt, J=2Hz, 8Hz), 8.24 (1H, d, J=7Hz), 8.31 (1H, d, J=6Hz), 8.72 (1H, d, J=2Hz), 10.79 (1H, s), 11.18 (1H, s)

its hydrochloride
mp : >250°C
NMR (DMSO-d_6, δ) : 5.50 (2H, s), 7.40-7.70 (5H, m), 7.75 (1H, dd, J=6Hz, 8Hz), 8.24 (1H, d, J=8Hz), 8.32 (1H, d, J=8Hz), 8.51 (1H, d, J=6Hz), 9.00 (1H, s), 11.19 (1H, s), 11.51 (1H, s)

(19) 4-(2,6-Dichlorobenzoylamino)-1-(morpholinocarbonyl)-

methyl-2-trifluoromethyl-1H-benzimidazole (from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and morpholine)
mp : 269-270°C
NMR (DMSO-d_6, δ) : 3.40-3.80 (8H, m), 5.50 (2H, s), 7.40-7.60 (5H, m), 8.23 (1H, d, J=8Hz), 11.15 (1H, s)

(20) 4-(2,6-Dichlorobenzoylamino)-1-(pyrrolidin-1-yl)carbonylmethyl-2-trifluoromethyl-1H-benzimidazole (from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and pyrrolidine)
mp : 148-150°C
NMR (DMSO-d_6, δ) : 1.94 (2H, m), 2.11 (2H, m), 3.50-3.60 (4H, m), 5.01 (2H, s), 7.12 (1H, d, J=8Hz), 7.30-7.40 (3H, m), 7.48 (1H, t, J=8Hz), 8.57 (1H, d, J=8Hz), 8.64 (1H, s)

(21) 4-(2,6-Dichlorobenzoylamino)-1-[N-(2-hydroxyethyl)-carbamoyl]methyl-2-trifluoromethyl-1H-benzimidazole (from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and (2-hydroxyethyl)amine)
mp : >250°C
NMR ($CDCl_3$, δ) : 3.38 (2H, t, J=7Hz), 3.62 (2H, t, J=7Hz), 4.99 (2H, s), 7.21 (1H, d, J=8Hz), 7.30-7.45 (3H, m), 7.51 (1H, t, J=8Hz), 8.59 (1H, d, J=8Hz)

(22) 1-[N,N-Bis(2-hydroxyethyl)carbamoyl]methyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and bis(2-hydroxyethyl)amine)
mp : >250°C

NMR ($CDCl_3$, δ) : 3.54 (2H, t, J=7Hz), 3.59 (2H, t, J=7Hz), 3.77 (2H, t, J=7Hz), 3.87 (2H, t, J=7Hz), 5.39 (2H, s), 7.18 (1H, d, J=8Hz), 7.30-7.50 (4H, m), 8.58 (1H, d, J=8Hz)

(23) 4-(2,6-Dichlorobenzoylamino)-1-[N-(ethoxycarbonylmethyl)carbamoyl]methyl-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and glycine ethyl ester)
mp : 228-230°C
NMR ($CDCl_3$, δ) : 1.26 (3H, t, J=7Hz), 4.02 (2H, d, J=5Hz), 4.20 (2H, q, J=7Hz), 5.03 (2H, s), 6.02 (1H, m), 7.22 (1H, d, J=8Hz), 7.31-7.43 (3H, m), 7.53 (1H, t, J=8Hz), 8.49-8.53 (2H, m)

(24) 4-(2,6-Dichlorobenzoylamino)-1-[N-(tetrahydrofuran-2-ylmethyl)carbamoyl]methyl-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-aminomethyltetrahydrofuran)
mp : 206-208°C
NMR ($CDCl_3$, δ) : 1.45 (1H, m), 1.77-1.99 (3H, m), 3.23 (1H, m), 3.54 (1H, m), 3.65 (2H, t, J=5Hz), 3.89 (1H, m), 4.87 (2H, s), 5.84 (1H, m), 7.20 (1H, d, J=8Hz), 7.31-7.42 (3H, m), 7.52 (1H, t, J=8Hz), 8.58-8.64 (2H, m)

(25) 1-[N-(Phenylsulfonyl)carbamoyl]methyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and benzenesulfonamide)
NMR ($CDCl_3$, δ) : 5.01 (2H, s), 6.93 (1H, d, J=8Hz),

7.31-7.45 (4H, m), 7.57 (2H, t, J=8Hz), 7.70 (1H, t, J=8Hz), 8.00 (2H, d, J=8Hz), 8.54 (2H, d, J=8Hz), 8.60 (1H, s)

(26) 4-(2,6-Dichlorobenzoylamino)-1-[N-(1,3-dihydroxy-2-propyl)carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 1,3-dihydroxy-2-aminopropane)
mp : 245-247°C
NMR (DMSO-d_6, δ) : 3.45 (4H, t, J=4Hz), 3.72 (1H, m), 4.72 (2H, t, J=4Hz), 5.14 (2H, s), 7.40-7.60 (5H, m), 815-8.30 (2H, m)

(27) 4-(2,6-Dichlorobenzoylamino)-1-[N-(2-furylmethyl)-carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-aminomethylfuran)
mp : 212-214°C
NMR ($CDCl_3$, δ) : 4.45 (2H, d, J=7Hz), 4.99 (2H, s), 5.78 (1H, m), 6.18 (1H, s), 6.30 (1H, s), 7.16 (1H, d, J=8Hz), 7.32 (1H, s), 7.33-7.45 (3H, m), 7.52 (1H, t, J=8Hz), 8.59 (1H, s), 8.61 (1H, d, J=8Hz)

(28) 4-(2,6-Dichlorobenzoylamino)-1-[N-(1,3,4-thiadiazol-2-yl)carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-amino-1,3,4-thiadiazole)
mp : >260°C
NMR (DMSO-d_6, δ) : 5.57 (2H, s), 7.40-7.65 (5H, m), 8.24 (1H, d, J=8Hz), 9.20 (1H, s)

(29) 4-(2,6-Dichlorobenzoylamino)-1-[N-(5-methoxypyridin-2-

yl)carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole hydrochloride
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-methoxy-5-aminopyridine)
mp : 202-210°C
NMR (DMSO-d_6, δ) : 3.82 (3H, s), 5.38 (2H, s), 6.83 (1H, d, J=9Hz), 7.40-7.65 (5H, m), 7.89 (1H, dd, J=4Hz, 9Hz), 8.23 (1H, d, J=8Hz), 8.35 (1H, d, J=4Hz)

(30) 4-(2,6-Dichlorobenzoylamino)-2-trifluoromethyl-1-[N-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)carbamoylmethyl]-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-amino-5-trifluoromethyl-1,3,4-thiadiazole)
mp : >250°C
NMR (DMSO-d_6, δ) : 5.62 (2H, s), 7.40-7.60 (5H, m), 8.25 (1H, d, J=8Hz), 11.20 (1H, s)

(31) 4-(2,6-Dichlorobenzoylamino)-1-[N-(5-methylisoxazol-3-yl)carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 3-amino-5-methylisoxazole
mp : 245-247°C
NMR ($CDCl_3$, δ) : 2.42 (3H, s), 5.21 (2H, s), 6.70 (1H, s), 7.18 (1H, d, J=8Hz), 7.3-7.5 (3H, m), 7.53 (1H, t, J=8Hz), 8.62 (1H, d, J=8Hz), 8.65 (1H, s)

(32) 4-(2,6-Dichlorobenzoylamino)-1-[N-(1,1-dimethyl-2-hydroxyethyl)carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-

trifluoromethyl-1H-benzimidazole and 2-amino-1-hydroxy-2-methylpropane)
mp : 242-244°C
NMR (DMSO-d_6, δ) : 1.19 (6H, s), 3.38 (2H, d, J=5Hz), 4.80 (1H, t, J=5Hz), 5.08 (2H, s), 7.40-7.60 (5H, m), 7.93 (1H, s), 8.22 (1H, m)

(33) 4-(2,6-Dichlorobenzoylamino)-1-[N-(4-methyloxazol-2-yl)carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-amino-4-methyloxazole)
mp : >250°C
NMR (DMSO-d_6, δ) : 2.05 (3H, s), 5.45 (2H, br s), 7.40-7.65 (6H, m), 8.23 (1H, d, J=8Hz), 11.18 (1H, s), 11.79 (1H, br s)

(34) 4-(2,6-Dichlorobenzoylamino)-2-trifluoromethyl-1-[N-(3-trifluoromethylbenzyl)carbamoylmethyl]-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 1-aminomethyl-3-trifluoromethylbenzene)
mp : 207-208°C
NMR (DMSO-d_6, δ) : 4.43 (2H, d, J=6Hz), 5.24 (2H, s), 7.40-7.70 (10H, m), 8.23 (1H, d, J=8Hz), 8.97 (1H, t, J=6Hz)

(35) 4-(2,6-Dichlorobenzoylamino)-1-[N-(pyridin-3-ylmethyl)carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole hydrochloride
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 3-aminomethylpyridine)
mp : 228-231°C
NMR (DMSO-d_6, δ) : 4.50 (2H, d, J=6Hz), 5.27 (2H, s),

7.40-7.60 (5H, m), 7.89 (1H, dd, J=6Hz, 8Hz), 8.23 (1H, d, J=8Hz), 8.27 (1H, d, J=8Hz), 8.70-8.80 (2H, m), 9.18 (1H, t, J=6Hz)

(36) 4-(2,6-Dichlorobenzoylamino)-1-[N-(pyridin-2-ylmethyl)carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole hydrochloride
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-aminomethylpyridine)
mp : >250°C
NMR (DMSO-d_6, δ) : 4.60 (2H, d, J=6Hz), 5.31 (2H, s), 7.40-7.70 (7H, m), 8.20-8.30 (2H, m), 8.71 (1H, d, J=6Hz), 9.23 (1H, t, J=6Hz)

(37) 4-(2,6-Dichlorobenzoylamino)-1-[N-[3,4-(methylenedioxy)-benzyl]carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 3,4-(methylenedioxy)benzylamine)
mp : 230-231°C
NMR (DMSO-d_6, δ) : 4.24 (2H, d, J=6Hz), 5.20 (2H, s), 6.00 (2H, s), 6.75 (1H, d, J=8Hz), 6.83 (1H, s), 6.88 (1H, d, J=8Hz), 7.40-7.60 (5H, m), 8.23 (1H, d, J=8Hz), 8.82 (1H, t, J=6Hz)

(38) 4-(2,6-Dichlorobenzoylamino)-1-(methoxycarbamoylmethyl)-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and methoxyamine hydrochloride)
mp : 235-236°C
NMR (DMSO-d_6, δ) : 3.61 and 3.79 (3H, s), 5.06 and 5.43 (2H, s), 7.40-7.60 (5H, m), 8.23 (1H, d,

J=8Hz)

(39) 4-(2,6-Dichlorobenzoylamino)-1-[N-[2-(indol-3-yl)ethyl]-carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 3-(2-aminoethyl)indole)
NMR ($CDCl_3$, δ) : 2.87 (2H, t, J=7Hz), 3.57 (2H, q, J=7Hz), 4.88 (2H, s), 5.29 (1H, br), 6.50 (1H, s), 6.99 (1H, d, J=8Hz), 7.07 (1H, t, J=8Hz), 7.20 (1H, t, J=8Hz), 7.30-7.50 (6H, m), 7.98 (1H, br s), 8.50 (1H, d, J=8Hz), 8.58 (1H, s)

(40) 4-(2,6-Dichlorobenzoylamino)-1-[N-[2-(pyridin-2-yl)ethyl]carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-(2-aminoethyl)pyridine)
mp : 174-176°C
NMR ($CDCl_3$, δ) : 2.81 (2H, t, J=6Hz), 3.63 (2H, q, J=6Hz), 5.98 (2H, s), 6.95-7.03 (2H, m), 7.15 (1H, d, J=8Hz), 7.32-7.53 (5H, m), 7.65 (1H, br), 7.82 (1H, d, J=4Hz), 8.60 (1H, d, J=8Hz), 8.65 (1H, s)

(41) 4-(2,6-Dichlorobenzoylamino)-1-[N-[2-(imidazol-4-yl)-ethyl]carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 4-(2-aminoethyl)imidazole)
NMR ($CDCl_3$, δ) : 2.22 (2H, t, J=7Hz), 3.47 (2H, q, J=7Hz), 4.95 (2H, s), 6.67 (1H, s), 7.12 (1H, d, J=8Hz), 7.30-7.53 (5H, m), 8.54 (1H, d, J=8Hz)

(42) 4-(2,6-Dichlorobenzoylamino)-1-[N-(3-hydroxypropyl)-

carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole (from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and (3-hydroxypropyl)-amine)

mp : 234-236°C

NMR (DMSO-d_6, δ) : 1.18 (2H, quint., J=7Hz), 3.16 (2H, q, J=7Hz), 3.43 (2H, q, J=7Hz), 4.44 (1H, t, J=7Hz), 5.10 (2H, s), 7.40-7.60 (5H, m), 8.22 (1H, dd, J=2Hz, 8Hz), 8.34 (1H, t, J=7Hz)

(43) 4-(2,6-Dichlorobenzoylamino)-1-[N-(3-methoxyphenyl)-carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole (from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 3-methoxyaniline)

mp : >250°C

NMR (DMSO-d_6, δ) : 3.71 (3H, s), 5.36 (2H, s), 6.68 (1H, d, J=8Hz), 7.08 (1H, d, J=8Hz), 7.20-7.30 (2H, m), 7.40-7.60 (5H, m), 8.24 (1H, d, J=8Hz)

(44) 4-(2,6-Dimethylbenzoylamino)-1-(morpholinocarbonyl)-methyl-2-trifluoromethyl-1H-benzimidazole (from 1-carboxymethyl-4-(2,6-dimethylbenzoylamino)-2-trifluoromethyl-1H-benzimidazole and morpholine)

mp : 246-247°C

NMR (DMSO-d_6, δ) : 2.35 (6H, s), 3.40-3.80 (8H, m), 5.50 (2H, s), 7.11 (2H, d, J=8Hz), 7.23 (1H, t, J=8Hz), 7.46 (1H, t, J=8Hz), 7.53 (1H, d, J=8Hz), 7.99 (1H, d, J=8Hz)

(45) 4-(2,6-Dichlorobenzoylamino)-1-[N-(3-dimethylaminophenyl)carbamoylmethyl]-2-trifluormethyl-1H-benzimidazole (from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and N,N-dimethyl-1,3-phenylenediamine)

mp : >250°C

NMR (DMSO-d_6, δ) : 2.85 (6H, s), 5.34 (2H, s), 6.56 (1H, d, J=8Hz), 6.84 (1H, d, J=8Hz), 7.01 (1H, s), 7.10 (1H, t, J=8Hz), 7.40-7.60 (5H, m), 8.23 (1H, d, J=8Hz)

(46) 4-(2,6-Dimethylbenzoylamino)-1-[N-(pyridin-3-ylmethyl)carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole hydrochloride
(from 1-carboxymethyl-4-(2,6-dimethylbenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 3-aminomethylpyridine)
mp : 195-200°C
NMR (DMSO-d_6, δ) : 2.33 (6H, s), 4.51 (2H, d, J=6Hz), 5.27 (2H, s), 7.11 (2H, d, J=8Hz), 7.24 (1H, t, J=8Hz), 7.48 (1H, t, J=8Hz), 7.56 (1H, d, J=8Hz), 7.92 (1H, dd, J=7Hz, 8Hz), 7.99 (1H, d, J=8Hz), 8.30 (1H, d, J=8Hz), 8.77 (1H, d, J=7Hz), 8.78 (1H, s), 9.21 (1H, t, J=6Hz)

(47) 4-(2,6-Dichlorobenzoylamino)-2-trifluoromethyl-1-[N-(4-trifluoromethylphenyl)carbamoylmethyl]-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 4-trifluoromethylaniline)
mp : >250°C
NMR ($CDCl_3$-CD_3OD, δ) : 5.60 (2H, s), 7.21 (1H, d, J=8Hz), 7.30-7.60 (6H, m), 7.65-7.75 (2H, m), 8.68 (1H, d, J=8Hz)

(48) 4-(2,6-Dichlorobenzoylamino)-1-[N-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 5-amino-1,3,4-

thiadiazole-2-sulfonamide)
mp : >250°C
NMR (DMSO-d_6, δ) : 5.57 (2H, s), 7.45-7.62 (5H, m), 8.24 (1H, d, J=8Hz), 8.32 (2H, s)

(49) 4-(2,6-Dichlorobenzoylamino)-1-[N-(5-ethylthio-1,3,4-thiadiazol-2-yl)carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-amino-5-ethylthio-1,3,4-thiadiazole)
mp : >250°C
NMR (DMSO-d_6, δ) : 1.32 (3H, t, J=7Hz), 3.21 (2H, q, J=7Hz), 5.55 (2H, s), 7.43-7.63 (5H, m), 8.24 (1H, d, J=8Hz)

(50) 4-(2,6-Dichlorobenzoylamino)-1-[N-(5-methyl-1,3,4-thiadiazol-2-yl)carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole
(from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 2-amino-5-methyl-1,3,4-thiadiazole)
mp : >250°C
NMR ($CDCl_3$:CD_3OD = 20:1, δ) : 2.69 (3H, s), 5.32 (2H, s), 7.21 (1H, d, J=8Hz), 7.30-7.45 (3H, m), 7.52 (1H, t, J=8Hz), 8.60 (1H, d, J=8Hz)

Example 16

A solution of 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (200 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (106 mg) and 1-hydroxybenzotriazole (75 mg) in N,N-dimethylformamide (2 ml) were stirred for 2 hours at ambient temperature, and to the mixture was added 2-trifluoromethylaniline (90 mg). After stirring for 2 days at 80°C, the mixture was poured

into ice-water and extracted with ethyl acetate. The extract was washed with 1N hydrochloric acid, brine and saturated sodium bicarbonate solution, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1-[N-(2-trifluoromethylphenyl)carbamoylmethyl]-1H-benzimidazole (100 mg) and 4-(2,6-dichlorobenzoylamino)-1-(N,N-dimethylcarbamoyl)methyl-2-trifluoromethyl-1H-benzimidazole (46 mg) as by-product.

4-(2,6-Dichlorobenzoylamino)-2-trifluoromethyl-1-[N-(2-trifluoromethylphenyl)carbamoylmethyl]-1H-benzimidazole

mp : >250°C

NMR ($CDCl_3$-CD_3OD, δ) : 5.20 (2H, s), 7.20-7.45 (5H, m), 7.50-7 70 (3H, m), 7.85 (1H, d, J=8Hz), 8.63 (1H, d, J=8Hz)

4-(2,6-Dichlorobenzoylamino)-1-(N,N-dimethylcarbamoyl)-methyl-2-trifluoromethyl-1H-benzimidazole

mp : 243-244°C

NMR ($CDCl_3$, δ) : 3.02 (3H, s), 3.18 (3H, s), 5.08 (2H, s), 7.09 (1H, d, J=8Hz), 7.28-7.40 (3H, m), 7.47 (1H, t, J=8Hz), 8.56 (1H, d, J=8Hz), 8.63 (1H, br s)

Example 17

A mixture of 1-(2-acetoxyethyl)-4-(2,6-dichlorobenzoyl-amino)-2-methyl-1H-benzimidazole (110 mg), 1N sodium hydroxide solution (0.5 ml) and methanol (5 ml) was refluxed for 30 minutes, and cold water was added thereto. The mixture was extracted with dichloromethane, and the extract was washed with brine, dried and concentrated in vacuo to give a residue containing 4-(2,6-dichlorobenzoylamino)-1-(2-hydroxyethyl)-2-methyl-1H-benzimidazole. The residue was dissolved in 10% methanolic hydrogen chloride, and the

solution was concentrated in vacuo to give 4-(2,6-dichlorobenzoylamino)-1-(2-hydroxyethyl)-2-methyl-1H-benzimidazole hydrochloride (85 mg).

mp : >250°C

NMR (DMSO-d_6, δ) : 2.87 (3H, s), 3.79 (2H, t, J=6Hz), 4.50 (2H, t, J=6Hz), 7.50-7.65 (4H, m), 7.73 (1H, d, J=7Hz), 8.09 (1H, d, J=7Hz)

Example 18

To 1M solution of methylmagnesium bromide in tetrahydrofuran (3 ml) was dropwise added a solution of 4-(2,6-dichlorobenzoylamino)-2-methyl-1-(2-oxopropyl)-1H-benzimidazole (188 mg) in tetrahydrofuran (1 ml), and the mixture was stirred for 3 hours at ambient temperature. The mixture was cooled to 4°C, and saturated ammonium chloride solution was dropwise added thereto. The mixture was adjusted to pH 8 with saturated sodium bicarbonate solution, and extracted with ethyl acetate. The extract was washed with brine, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give 4-(2,6-dichlorobenzoylamino)-1-(2-hydroxy-2-methylpropyl)-2-methyl-1H-benzimidazole. It was dissolved in 10% methanolic hydrogen chloride, and the solution was concentrated in vacuo to give 4-(2,6-dichlorobenzoylamino)-1-(2-hydroxy-2-methylpropyl)-2-methyl-1H-benzimidazole hydrochloride (108 mg).

mp : >250°C

NMR (DMSO-d_6, δ) : 1.21 (6H, s), 2.37 (3H, s), 4.37 (2H, s), 7.50-7.65 (4H, m), 7.79 (1H, d, J=7Hz), 8.12 (1H, d, J=7Hz)

Example 19

4-(2,6-Dichlorobenzoylamino)-1-(2-hydroxy-2-methylpropyl)-2-trifluoromethyl-1H-benzimidazole was obtained by reacting 4-(2,6-dichlorobenzoylamino)-1-(2-oxopropyl)-2-trifluoromethyl-1H-benzimidazole with methylmagnesium bromide

according to a similar manner to that of Example 18.

mp : >250°C

NMR (DMSO-d_6, δ) : 1.16 (6H, s), 4.37 (2H, s), 4.85 (1H, s), 7.40-7.60 (4H, m), 7.67 (1H, d, J=8Hz), 8.21 (1H, d, J=8Hz), 11.10 (1H, s)

Example 20

Acetic anhydride (62 mg) was added to a solution of 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole (128 mg) in acetic acid (1 ml). The solution was stirred at ambient temperature overnight and evaporated in vacuo. The residue was crystallized from ethyl acetate to give 1-acetyl-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole (93 mg).

mp : 143-145°C

NMR ($CDCl_3$, δ) : 2.82 (6H, s), 7.30-7.45 (4H, m), 7.48 (1H, d, J=7Hz), 8.53 (1H, d, J=7Hz), 8.58 (1H, br s)

Example 21

4-(2,6-Dichlorobenzoylamino)-1-(2-hydroxyethyl)-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 17.

mp : 183-185°C

NMR ($CDCl_3$, δ) : 1.94 (1H, t, J=6Hz), 4.04 (2H, q, J=6Hz), 4.49 (2H, t, J=6Hz), 7.30-7.45 (4H, m), 7.48 (1H, t, J=7.5Hz), 8.56 (1H, d, J=7.5Hz), 8.67 (1H, br s)

Example 22

To a suspension of 4-(2,6-dichlorobenzoylamino)-2-methyl-1-(2-oxopropyl)-1H-benzimidazole (188 mg) in methanol (5 ml) was added sodium borohydride (38 mg), and the mixture was stirred for 2 hours at ambient temperature. Water was added thereto, and the precipitate was collected by filtration, washed with water and dried to give 4-(2,6-

dichlorobenzoylamino)-1-(2-hydroxypropyl)-2-methyl-1H-benzimidazole (155 mg).

mp : >250°C

NMR ($CDCl_3$-CD_3OD, δ) : 1.22 (3H, d, J=6Hz), 2.53 (3H, s), 3.99 (2H, m), 4.10 (1H, m), 7.07 (1H, d, J=7Hz), 7.20-7.45 (4H, m), 8.33 (1H, d, J=7Hz)

Example 23

The following compounds were obtained according to a similar manner to that of Example 22.

(1) 4-(2,6-Dichlorobenzoylamino)-1-(2-hydroxy-2-phenylethyl)-2-methyl-1H-benzimidazole hydrochloride (from 1-benzoylmethyl-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole)

NMR (DMSO-d_6, δ) : 2.80 (3H, s), 4.44-4.69 (2H, m), 5.05 (1H, m), 7.30-7.45 (3H, m), 7.48-7.65 (6H, m), 7.75 (1H, d, J=8Hz), 8.10 (1H, d, J=8Hz)

(2) 4-(2,6-Dichlorobenzoylamino)-1-[2-hydroxy-2-(pyridin-4-yl)ethyl]-2-trifluoromethyl-1H-benzimidazole (from 4-(2,6-dichlorobenzoylamino)-1-(pyridin-4-yl)-carbonylmethyl-2-trifluoromethyl-1H-benzimidazole)

mp : 230-232°C

NMR (DMSO-d_6, δ) : 4.43 (1H, dd, J=8Hz, 15Hz), 4.62 (1H, dd, J=4Hz, 15Hz), 4.90-5.10 (1H, m), 6.03 (1H, m), 7.40-7.60 (6H, m), 7.67 (1H, d, J=8Hz), 8.23 (1H, d, J=8Hz), 8.58 (2H, d, J=8Hz), 11.14 (1H, s)

its hydrochloride

mp : 225-227°C

NMR (DMSO-d_6, δ) : 4.47 (1H, dd, J=8Hz, 15Hz), 4.76 (1H, dd, J=4Hz, 15Hz), 5.26 (1H, dd, J=4Hz, 8Hz), 6.44 (1H, br s), 7.40-7.60 (4H, m), 7.23 (1H, d, J=8Hz), 8.06 (2H, d, J=7Hz), 8.24 (1H, d, J=8Hz),

8.89 (2H, d, J=7Hz), 11.14 (1H, s)

(3) 4-(2,6-Dichlorobenzoylamino)-1-[2-hydroxy-2-(pyridin-3-yl)ethyl]-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-1-(pyridin-3-yl)carbonylmethyl-2-trifluoromethyl-1H-benzimidazole)
mp : 205-207°C
NMR (DMSO-d_6, δ) : 4.52 (1H, dd, J=8Hz, 15Hz), 4.61 (1H, dd, J=4Hz, 15Hz), 5.00-5.10 (1H, m), 5.98 (1H, s), 7.40-7.60 (5H, m), 7.64 (1H, d, J=8Hz), 7.86 (1H, d, J=8Hz), 8.22 (1H, d, J=8Hz), 8.53 (1H, d, J=6Hz), 8.63 (1H, s), 11.13 (1H, s)

its hydrochloride
mp : 217-227°C
NMR (DMSO-d_6, δ) : 4.53 (1H, dd, J=8Hz, 15Hz), 4.73 (1H, dd, J=4Hz, 15Hz), 5.22 (1H, dd, J=4Hz, 8Hz), 6.30 (1H, br s), 7.40-7.60 (4H, m), 7.70 (1H, d, J=8Hz), 7.91 (1H, dd, J=7Hz, 8Hz), 8.23 (1H, d, J=8Hz), 8.45 (1H, d, J=8Hz), 8.80 (1H, d, J=7Hz), 8.93 (1H, s), 11.15 (1H, s)

(4) 4-(2,6-Dichlorobenzoylamino)-1-(2-hydroxypropyl)-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-1-(2-oxopropyl)-2-trifluoromethyl-1H-benzimidazole)
mp : 234-234.5°C
NMR ($CDCl_3$, δ) : 1.34 (3H, d, J=6Hz), 2.03 (1H, d, J=6Hz), 4.20-4.40 (3H, m), 7.30-7.45 (4H, m), 7.46 (1H, t, J=7.5Hz), 8.55 (1H, d, J=7.5Hz), 8.74 (1H, br s)

Example 24

(1) A mixture of 4-(2,6-dichlorobenzoylamino)-1-(2-hydroxyethyl)-2-methyl-1H-benzimidazole (95 mg), carbon

tetrabromide (100 mg) and triphenyl phosphine (99 mg) in dichloromethane was stirred at ambient temperature for 1 day. The mixture was evaporated in vacuo and the residue was purified by column chromatography on silica gel. The obtained oil was crystallized from diisopropyl ether to give 1-(2-bromoethyl)-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole (42 mg).

NMR ($CDCl_3$, δ) : 2.66 (3H, s), 3.70 (2H, t, J=8Hz), 4.55 (2H, t, J=8Hz), 7.12 (1H, d, J=8Hz), 7.24-7.42 (4H, m), 8.49 (1H, d, J=8Hz), 8.59 (1H, s)

(2) To a solution of 1-(2-bromoethyl)-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole (37 mg) in N,N-dimethylformamide (0.5 ml) were added 4-mercaptopyridine (11 mg), potassium carbonate (25 mg) and potassium iodide (28 mg), and the mixture was stirred for 5 hours at ambient temperature. The mixture was partitioned between ethyl acetate and water, and the organic layer was washed with water and brine, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (2% methanol-dichloromethane) to give 4-(2,6-dichlorobenzoylamino)-2-methyl-1-[2-(pyridin-4-ylthio)ethyl]-1H-benzimidazole (38 mg).

mp : 229-231°C

NMR ($CDCl_3$, δ) : 2.55 (3H, s), 3.42 (2H, t, J=7Hz), 4.42 (2H, t, J=7Hz), 7.05-7.10 (3H, m), 7.25-7.40 (4H, m), 8.42 (2H, d, J=5Hz), 8.47 (1H, d, J=8Hz), 8.55 (1H, s)

Example 25

4-(2,6-Dichlorobenzoylamino)-2-methyl-1-[3-(pyridin-4-ylthio)propyl]-1H-benzimidazole was obtained by reacting 1-(3-chloropropyl)-4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole with 4-mercaptopyridine according to a similar manner to that of Example 24-(2).

NMR ($CDCl_3$, δ) : 2.18-2.29 (2H, m), 2.57 (3H, s), 2.99 (2H, t, J=7Hz), 4.30 (2H, t, J=7Hz), 7.05-7.12 (3H, m), 7.25-7.40 (4H, m), 8.38-8.45 (3H, m), 8.57 (1H, s)

Example 26

Bromine (93 mg) was added to a solution of 4-(2,6-dichlorobenzoylamino)-2-methyl-1-(2-oxopropyl)-1H-benzimidazole (200 mg) in dichloromethane (2 ml). The solution was stirred at ambient temperature for 15 minutes and diluted with dichloromethane. Then, the solution was washed with aqueous sodium thiosulfate and aqueous saturated sodium bicarbonate, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diisopropyl ether to give 7-bromo-4-(2,6-dichlorobenzoylamino)-2-methyl-1-(2-oxopropyl)-1H-benzimidazole (220 mg).

mp : >250°C

NMR ($CDCl_3$, δ) : 2.33 (3H, s), 2.45 (3H, s), 5.31 (2H, s), 7.28-7.40 (4H, m), 8.32 (1H, d, J=8Hz), 8.55 (1H, s)

Example 27

(1) 1-(2-tert-Butoxycarbonylhydrazino)carbonylmethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole was obtained from 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and tert-butoxycarbonylhydrazine according to a similar manner to that of Example 14.

mp : 160-164°C

NMR ($CDCl_3$, δ) : 1.56 and 1.59 (9H, s), 5.05 and 5.17 (2H, s), 6.41 and 6.55 (1H, s), 7.10-7.60 (5H, m), 8.50-8.65 (2H, m)

(2) A mixture of 1-(2-tert-butoxycarbonylhydrazino)-carbonylmethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (244 mg) and 4N solution of hydrogen chloride in ethyl acetate was stirred for 2 hours at ambient temperature. The mixture was concentrated in vacuo, and the residue was triturated with diethyl ether to give 4-(2,6-dichlorobenzoylamino)-1-hydrazinocarbonylmethyl-2-trifluoromethyl-1H-benzimidazole hydrochloride (186 mg).

mp : >250°C

NMR (CD_3OD, δ) : 5.33 (2H, s), 7.40-7.60 (5H, m), 8.40 (1H, d, J=8Hz)

Example 28

A mixture of 4-(2,6-dichlorobenzoylamino)-1-(2-phthalimidoethyl)-2-trifluoromethyl-1H-benzimidazole (462 mg) and hydrazine monohydrate (63.4 mg) in ethanol was refluxed for 5 hours. The mixture was cooled and insoluble material was filtered off. The filtrate was concentrated in vacuo and the residue was triturated with ethanol to give 1-(2-aminoethyl)-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (160 mg).

mp : 188-190°C

NMR (DMSO-d_6, δ) : 2.93 (2H, t, J=7Hz), 4.35 (2H, t, J=7Hz), 7.40-7.60 (4H, m), 7.64 (1H, d, J=8Hz), 8.21 (1H, d, J=8Hz)

Example 29

4-(2,6-Dichlorobenzoylamino)-1-[2-(morpholinocarbonylamino)ethyl]-2-trifluoromethyl-1H-benzimidazole was obtained by reacting 1-(2-aminoethyl)-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole with morpholinocarbonyl chloride.

mp : 222-223°C

NMR (DMSO-d_6, δ) : 3.10-3.20 (4H, m), 3.40-3.50 (6H, m), 4.40-4.50 (2H, m), 6.77 (1H, m), 7.40-7.60 (5H,

m), 8.23 (1H, m), 11.12 (1H, s)

Example 30

To a solution of 1-(2-aminoethyl)-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (114 mg) in pyridine was added mesyl chloride (37.6 mg) and the mixture was stirred for 1 hour at ambient temperature. Mesyl chloride (37.6 mg) was further added thereto, and the mixture was stirred for 1 hour at the same temperature. The mixture was poured into water and extracted with ethyl acetate. The extract was washed with 3.6% hydrochloric acid, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated in vacuo to give a solid. The solid was treated with ethanol and filtered. The filtrate was concentrated and the residue was crystallized from dichloromethane - n-hexane to give 4-(2,6-dichlorobenzoylamino)-1-(2-methylsulfonylaminoethyl)-2-trifluoromethyl-1H-benzimidazole (54.7 mg).

mp : 178-180°C

NMR (DMSO-d_6, δ) : 2.87 (3H, s), 3.39 (2H, q, J=7Hz), 4.50 (2H, t, J=7Hz), 7.33 (1H, t, J=7Hz), 7.40-7.60 (5H, m), 8.23 (1H, d, J=8Hz)

Example 31

To a solution of 1-(2-aminoethyl)-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (105 mg) in pyridine was added acetic anhydride (77.1 mg) and the mixture was stirred for 1 hour at ambient temperature. The mixture was poured into water and extracted with ethyl acetate. The extract was washed with 3.6% hydrochloric acid, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated in vacuo to give 1-(2-acetylaminoethyl)-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (72.9 mg).

mp : 222-224°C

NMR (DMSO-d_6, δ) : 1.69 (3H, s), 3.48 (2H, q, J=7Hz), 4.45 (2H, t, J=7Hz), 7.40-7.60 (5H, m), 8.06 (1H, t, J=7Hz), 8.24 (1H, m)

Example 32

A mixture of 4-(2,6-dichlorobenzoylamino)-2-methyl-1H-benzimidazole (200 mg), methyl acrylate (538 mg) and sodium carbonate (132 mg) in N,N-dimethylformamide (4 ml) was stirred at 100°C for 24 hours. The mixture was poured into a mixture of ice and water and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained amorphous was dissolved in methanolic hydrogen chloride. The solution was evaporated in vacuo and the residue was crystallized from 2-propanol to give 4-(2,6-dichlorobenzoylamino)-1-(2-methoxycarbonylethyl)-2-methyl-1H-benzimidazole hydrochloride (51 mg).

mp : 208-210°C

NMR ($CDCl_3$, δ) : 2.94-3.02 (5H, m), 3.68 (3H, s), 4.58 (2H, t, J=5Hz), 7.20-7.40 (4H, m), 7.54 (1H, t, J=8Hz), 8.81 (1H, d, J=8Hz), 11.30 (1H, m)

Example 33

A mixture of 4-(2,6-dichlorobenzoylamino)-2-methyl-1-(2-oxopropyl)-1H-benzimidazole (100 mg) and 2-hydrazinopyridine (29 mg) in ethanol (2 ml) was stirred at 50°C for 1 hour. The mixture was cooled and the resulting solid was collected. The obtained solid was dissolved in methanolic hydrogen chloride and the solution was evaporated in vacuo. The crystalline residue was triturated with 2-propanol to give 4-(2,6-dichlorobenzoylamino)-2-methyl-1-[2-(pyridin-2-ylhydrazono)propyl]-1H-benzimidazole dihydrochloride (99 mg).

mp : 210-213°C

NMR (DMSO-d_6, δ) : 2.10 (3H, s), 2.84 (3H, s), 5.35

(2H, s), 7.10 (1H, t, J=8Hz), 7.40 (1H, m), 7.48-7.62 (4H, m), 7.75 (1H, d, J=8Hz), 8.05 (1H, t, J=8Hz), 8.12-8.20 (2H, m), 11.34 (1H, br s), 11.92 (1H, m)

Example 34

A mixture of 1-cyanomethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (200 mg) and trimethyltin azide (299 mg) in xylene (4 ml) was stirred at 120°C for 18 hours. To the reaction mixture was added dichloromethane and methanol to give a clear solution. Silica gel (2 g) was added to the solution and the mixture was stirred for 30 minutes and filtered. The filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel. The obtained oil was crystallized from a mixture of 2-propanol and water to yield 4-(2,6-dichlorobenzoylamino)-1-(1H-tetrazol-5-yl)methyl-2-trifluoromethyl-1H-benzimidazole (103 mg).

mp : 228-231°C

NMR (DMSO-d_6, δ) : 6.03 (2H, s), 7.44-7.58 (5H, m), 8.25 (1H, d, J=8Hz)

Example 35

(1) To a mixture of hydroxylamine hydrochloride (42 mg) and sodium carbonate (64 mg) in water (0.4 ml) and ethanol (7.4 ml) was added 1-cyanomethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (200 mg), and the mixture was refluxed for 1 hour. After cooling, water was added thereto, and the resulting precipitate was collected by filtration. The residue was purified by column chromatography to give 4-(2,6-dichlorobenzoylamino)-1-(N-hydroxyamidino)methyl-2-trifluoromethyl-1H-benzimidazole (150 mg).

mp : 235-236°C

NMR ($CDCl_3$, δ) : 4.48-4.53 (2H, m), 4.46 (2H, s), 6.52

(1H, m), 7.31-7.45 (4H, m), 7.51 (1H, t, J=8Hz), 8.60 (1H, d, J=8Hz), 8.65 (1H, br s)

(2) To a solution of 4-(2,6-dichlorobenzoylamino)-1-(N-hydroxyamidino)methyl-2-trifluoromethyl-1H-benzimidazole (56 mg) in acetic acid (1 ml) was added acetic anhydride (15 mg) at ambient temperature, and the mixture was stirred for 30 minutes at the same temperature, and then for 2 hours at 110°C. After cooling, methanol was added thereto, and the mixture was concentrated in vacuo to give 4-(2,6-dichlorobenzoylamino)-1-(5-methyl-1,2,4-oxadiazol-3-yl)methyl-2-trifluoromethyl-1H-benzimidazole (57 mg).

mp : 148-150°C

NMR ($CDCl_3$, δ) : 2.57 (3H, s), 5.58 (2H, s), 7.29-7.42 (4H, m), 7.50 (1H, t, J=8Hz), 8.58-8.61 (2H, m)

Example 36

1-[N-(Carboxymethyl)carbamoylmethyl]-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole was obtained from 4-(2,6-dichlorobenzoylamino)-1-[N-(ethoxycarbonylmethyl)carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole according to a similar manner to that of Example 11.

mp : >250°C

NMR (DMSO-d_6, δ) : 3.83 (2H, d, J=6Hz), 5.19 (2H, s), 7.40-7.60 (5H, m), 8.22 (1H, d, J=8Hz), 8.73 (1H, t, J=6Hz)

Example 37

4-(2,6-Dichlorobenzoylamino)-1-[N-[N-(2-hydroxyethyl)carbamoylmethyl]carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole was obtained from 1-[N-(carboxymethyl)carbamoylmethyl]-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and (2-hydroxyethyl)amine according to a similar manner to that of Example 13.

mp : >250°C

NMR (DMSO-d_6, δ) : 3.15 (2H, q, J=7Hz), 3.40 (2H, q, J=7Hz), 3.77 (2H, d, J=7Hz), 4.69 (1H, t, J=7Hz), 5.21 (2H, s), 7.40-7.60 (5H, m), 7.95 (1H, t, J=7Hz), 8.23 (1H, m), 8.63 (1H, t, J=7Hz)

Example 38

A mixture of 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (200 mg), oxalyl chloride (117 mg) and N,N-dimethylformamide (1 drop) in dichloromethane was stirred at ambient temperature for 1 hour. The mixture was evaporated in vacuo and the residue was dissolved in dichloromethane (2 ml). This solution was added dropwise to a solution of acetylhydrazine (86 mg) in dichloromethane. The mixture was stirred at ambient temperature for 2 hours, washed with 1N-hydrochloric acid, aqueous saturated sodium bicarbonate and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was crystallized from a mixture of 2-propanol and diisopropyl ether. The obtained crystal was added to phosphorus oxychloride (1.5 ml) and the mixture was refluxed for 2 hours. The reaction mixture was evaporated in vacuo, diluted with cold water, neutralized with aqueous saturated sodium bicarbonate and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was crystallized from a mixture of 2-propanol and water to give 4-(2,6-dichlorobenzoylamino)-1-(5-methyl-1,3,4-oxadiazol-2-ylmethyl)-2-trifluoromethyl-1H-benzimidazole (74 mg).

mp : 200-202°C

NMR ($CDCl_3$, δ) : 2.49 (3H, s), 5.68 (2H, s), 7.30-7.45 (4H, m), 7.53 (1H, t, J=8Hz), 8.57 (1H, br s), 8.60 (1H, d, J=8Hz)

Example 39

4-(2,6-Dichlorobenzoylamino)-1-[N-(5-methyl-1,3,4-oxadiazol-2-ylmethyl)carbamoylmethyl]-2-trifluromethyl-1H-benzimidazole was obtained from 1-[N-(carboxymethyl)-carbamoylmethyl]-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole according to a similar manner to that of Example 38.

mp : 156-158°C

NMR (DMSO-d_6, δ) : 2.48 (3H, s), 4.54 (2H, d, J=6Hz), 5.21 (2H, s), 7.35-7.60 (5H, m), 8.23 (1H, d, J=8Hz), 9.13 (1H, t, J=6Hz)

Example 40

To a mixture of 4-(2,6-dichlorobenzoylamino)-1-[N-(2-hydroxyethyl)carbamoyl]methyl-2-trifluoromethyl-1H-benzimidazole (143 mg), acetic anhydride (37 mg) and pyridine (31 mg) in dichloromethane (3 ml) was added N,N-dimethyl-aminopyridine (3 mg), and the mixture was stirred for 3 hours at ambient temperature. The mixture was concentrated in vacuo, and the residue was crystallized from methanol-water to give 1-[N-(2-acetoxyethyl)carbamoylmethyl]-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (135 mg).

mp : 214-215°C

NMR ($CDCl_3$-CD_3OD, δ) : 1.98 (3H, s), 3.49 (2H, t, J=6Hz), 4.13 (2H, t, J=6Hz), 4.97 (2H, s), 7.19 (1H, d, J=8Hz), 7.30-7.45 (3H, s), 7.52 (1H, t, J=8Hz), 8.60 (1H, d, J=8Hz)

Example 41

1-[N-(1,3-Diacetoxy-2-propyl)carbamoylmethyl]-4-(2,6-dichlorobenzoylamino)-2-trifluromethyl-1H-benzimidazole was obtained by reacting 4-(2,6-dichlorobenzoylamino)-1-[N-(1,3-dihydroxy-2-propyl)carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole with acetic anhydride according to a similar manner to that of Example 40.

mp : 162-164°C

NMR (DMSO-d_6, δ) : 2.02 (6H, s), 4.07 (4H, m), 4.25 (1H, m), 5.16 (2H, s), 7.40-7.60 (5H, m), 8.23 (1H, m), 8.59 (1H, d, J=8Hz)

Example 42

A mixture of 4-(2,6-dichlorobenzoylamino)-1-[N-(2-hydroxyethyl)carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole (180 mg) in thionyl chloride was stirred overnight at ambient temperature. After concentration, ice water was added to the residue, and extracted with ethyl acetate. The extract was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated in vacuo. The residue was dissolved in N,N-dimethylformamide, and imidazole (77.4 mg) and potassium iodide (6.29 mg) were added thereto. The mixture was stirred for 1 hour at 120°C, and then ethyl acetate was added thereto. The mixture was washed with water and brine, dried and concentrated in vacuo to give 4-(2,6-dichlorobenzoyl-amino)-1-[N-[2-(imidazol-1-yl)ethyl]carbamoylmethyl]-2-trifluoromethyl-1H-benzimidazole (103 mg).

mp : >250°C

NMR ($CDCl_3$, δ) : 3.54 (2H, t, J=7Hz), 4.06 (2H, t, J=7Hz), 4.93 (2H, s), 6.83 (1H, s), 6.95 (1H, s), 7.09 (1H, d, J=8Hz), 7.24 (1H, s), 7.30-7.50 (3H, m), 7.51 (1H, t, J=8Hz), 8.58 (1H, d, J=8Hz)

Example 43

4-(2,6-Dichlorobenzoylamino)-1-[2-(imidazol-1-yl)ethyl]-2-trifluoromethyl-1H-benzimidazole was obtained from 4-(2,6-dichlorobenzoylamino)-1-(2-hydroxyethyl)-2-trifluoromethyl-1H-benzimidazole and imidazole according to a similar manner to that of Example 42.

mp : 251-253°C

NMR (DMSO-d_6, δ) : 4.47 (2H, t, J=6Hz), 4.74 (2H, t,

J=6Hz), 6.81 (1H, s), 6.99 (1H, s), 7.24 (1H, d, J=8Hz), 7.35-7.60 (5H, m), 8.20 (1H, d, J=8Hz)

Example 44

(1) A mixture of 4-(2,6-dichlorobenzoylamino)-1-(2-hydroxyethyl)-2-trifluoromethyl-1H-benzimidazole (418 mg), glutaric anhydride (137 mg), pyridine (103 mg), catalytic amount of N,N-dimethylaminopyridine in dichloromethane (10 ml) was stirred overnight at ambient temperature. The mixture was washed with 1N hydrochloric acid and brine, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel and crystallized from diisopropyl ether to give 1-[2-(4-carboxybutanoyloxy)ethyl]-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (220 mg).

mp : 173-175°C

NMR ($CDCl_3$-CD_3OD, δ) : 1.86 (2H, quint., J=7Hz), 2.23-2.35 (4H, m), 4.49 (2H, t, J=6Hz), 4.62 (2H, t, J=6Hz), 7.27-7.45 (4H, m), 7.53 (1H, t, J=8Hz), 8.58 (1H, d, J=8Hz)

(2) A mixture of 1-[2-(4-carboxybutanoyloxy)ethyl]-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (215 mg), disuccinimidyl carbonate (207 mg) and pyridine (96 mg) in acetonitrile (20 ml) was stirred overnight at ambient temperature. To the mixture was added disuccinimidyl carbonate (103 mg), and the mixture was stirred for 1 day at the same temperature. The mixture was concentrated, and the insoluble material was filtered off. The filtrate was washed with saturated sodium bicarbonate solution, dried and concentrated in vacuo to give 4-(2,6-dichlorobenzoylamino)-1-[2-[4-(succinimidooxycarbonyl)butanoyloxy]ethyl]-2-trifluoromethyl-1H-benzimidazole (274 mg).

NMR ($CDCl_3$, δ) : 1.98 (2H, quint., J=7Hz), 2.40 (2H, t, J=7Hz), 2.64 (2H, t, J=7Hz), 2.84 (4H, s), 4.48

(2H, t, J=6Hz), 4.60 (2H, t, J=6Hz), 7.25-7.43 (4H, m), 7.52 (1H, t, J=8Hz), 8.58 (1H, d, J=8Hz), 8.60 (1H, s)

(3) To a mixture of aminomethylenebis(phosphonic acid) (77 mg) and triethylamine (162 mg) in N,N-dimethylformamide (2 ml) and water (0.5 ml) was added a solution of 4-(2,6-dichlorobenzoylamino)-1-[2-[4-(succinimidooxycarbonyl)-butanoyloxy]ethyl]-2-trifluoromethyl-1H-benzimidazole (126 mg) in N,N-dimethylformamide (1 ml), and the mixture was stirred overnight at ambient temperature. To the residue was added 1N hydrochloric acid (1.6 ml), and the mixture was concentrated. The residue was treated according to a usual manner to give [4-[2-[4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazol-1-yl]ethyloxycarbonyl]-butanoylaminomethylene]bis(phosphonic acid) (31 mg).

NMR (DMSO-d_6, δ) : 1.61 (2H, quint., J=7Hz), 2.10-2.25 (4H, m), 4.35-4.55 (3H, m), 4.70 (2H, t, J=6Hz), 7.42-7.57 (4H, m), 7.62 (1H, d, J=8Hz), 7.82 (1H, br d, J=8Hz), 8.22 (1H, d, J=8Hz)

Example 45

To a solution of 4-carboxy-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole (100 mg) in dichloromethane (1 ml) was added oxalyl chloride (71 mg), and the mixture was stirred for 10 minutes and then concentrated. To the residue were added 2-chloro-6-methylaniline (44 mg), triethylamine (57 mg) and dichloromethane (2 ml), and the mixture was stirred for 15 minutes. The mixture was washed with 1N sodium hydroxide solution, brine, 1N hydrochloric acid and brine, dried and concentrated to give 4-[N-(2-chloro-6-methylphenyl)carbamoyl]-1-(morpholinocarbonyl)-methyl-2-trifluoromethyl-1H-benzimidazole (98 mg).

mp : >250°C

NMR (DMSO-d_6, δ) : 2.30 (3H, s), 3.40-3.51 (2H, m),

3.55-3.78 (6H, m), 5.65 (2H, s), 7.27-7.38 (2H, m), 7.46 (1H, dd, J=8Hz, 2Hz), 7.69 (1H, t, J=8Hz), 8.09-8.18 (2H, m)

Example 46

The following compounds were obtained according to a similar manner to that of Example 45.

(1) 4-[N-(2-Methoxy-6-methylphenyl)carbamoyl]-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole
mp : 240-246°C
NMR (DMSO-d_6, δ) : 2.23 (3H, s), 3.42-3.50 (2H, m), 3.56-3.75 (6H, m), 3.78 (3H, s), 5.64 (2H, s), 6.92 (1H, d, J=8Hz), 6.97 (1H, d, J=8Hz), 7.22 (1H, t, J=8Hz), 7.67 (1H, t, J=8Hz), 8.09 (1H, d, J=8Hz), 8.13 (1H, d, J=8Hz)

(2) 4-[N-(2,6-Dimethylphenyl)carbamoyl]-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole
mp : >250°C
NMR (DMSO-d_6, δ) : 2.28 (6H, s), 3.44-3.50 (2H, m), 3.57-3.75 (6H, m), 5.64 (2H, s), 7.18 (3H, s), 7.68 (1H, t, J=8Hz), 8.07-8.13 (2H, m)

Example 47

(1) 2-Hydroxymethyl-4-nitro-1H-benzimidazole was obtained by reacting 3-nitro-1,2-phenylenediamine with glycolic acid according to a similar manner to that of Example 3-(1).
mp : 206-207°C
NMR (DMSO-d_6, δ) : 4.75 (2H, s), 5.63 (1H, br s), 7.39 (1H, t, J=7.5Hz), 8.05 (1H, d, J=7.5Hz), 8.11 (1H, d, J=7.5Hz)

(2) 2-Hydroxymethyl-4-nitro-1-(2-oxopropyl)-1H-benzimidazole was obtained by reacting 2-hydroxymethyl-4-nitro-1H-benzimidazole with 2-oxopropyl chloride according to a similar manner to that of Example 5.
mp : 128-129°C

(3) 4-Amino-2-hydroxymethyl-1-(2-oxopropyl)-1H-benzimidazole was obtained according to a similar manner to that of Example 1-(1).
mp : 120-121°C

(4) 4-(2,6-Dichlorobenzoylamino)-2-hydroxymethyl-1-(2-oxopropyl)-1H-benzimidazole was obtained according to a similar manner to that of Example 1-(2).
mp : >250°C
NMR (DMSO-d_6, δ) : 2.24 (3H, s), 4.63 (2H, d, J=7.5Hz), 5.32 (2H, s), 5.63 (1H, t, J=7.5Hz), 7.10-7.30 (2H, m), 7.40-7.60 (3H, m), 8.05 (1H, d, J=7.5Hz), 10.83 (1H, s)

Example 48

(1) 4-(2,6-Dimethylbenzoylamino)-2-trifluoromethyl-1H-benzimidazole was obtained by reacting 4-amino-2-trifluoromethyl-1H-benzimidazole with 2,6-dimethylbenzoyl chloride according to a similar manner to that of Example 1-(2).
mp : 234-235°C

(2) 4-(2,6-Dimethylbenzoylamino)-1-(2-oxopropyl)-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 5.
mp : 206-207°C
NMR (DMSO-d_6, δ) : 2.34 (3H, s), 5.55 (2H, s), 7.00-7.20 (2H, m), 7.24 (1H, t, J=8Hz), 7.45 (1H, t, J=8Hz), 7.51 (1H, d, J=8Hz), 7.98 (1H, d, J=8Hz),

10.45 (1H, s)

(3) 1-(tert-Butoxycarbonyl)methyl-4-(2,6-dimethylbenzoylamino)-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 5.

mp : 145-146°C

NMR ($CDCl_3$, δ) : 1.44 (9H, s), 2.41 (6H, s), 4.92 (2H, s), 7.00-7.15 (3H, m), 7.23 (1H, d, J=8Hz), 7.50 (14H, t, J=8Hz), 8.54 (1H, s), 8.60 (1H, d, J=8Hz)

Example 49

(1) 4-(2,6-Dimethoxybenzoylamino)-2-trifluoromethyl-1H-benzimidazole was obtained by reacting 4-amino-2-trifluoromethyl-1H-benzimidazole with 2,6-dimethoxybenzoyl chloride according to a similar manner to that of Example 1-(2).

mp : 214-215°C

(2) 4-(2,6-Dimethoxybenzoylamino)-1-(2-oxopropyl)-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 5.

mp : 226-227°C

NMR (DMSO-d_6, δ) : 2.32 (3H, s), 3.76 (6H, s), 5.54 (2H, s), 6.73 (2H, d, J=8Hz), 7.37 (1H, t, J=8Hz), 7.40-7.50 (2H, m), 8.22 (1H, m), 9.95 (1H, s)

Example 50

(1) A suspension of 2-hydroxymethyl-4-nitro-1H-benzimidazole (300 mg) in aqueous 0.5N sodium hydroxide (3.2 ml) was stirred at 110°C and to the suspension was added dropwise a solution of potassium permanganate (368 mg) in hot water (10 ml). The mixture was stirred at 110°C for 20 minutes and the insoluble solid was filtered and washed with hot water and a small amount of hot aqueous 1N sodium hydroxide. The

filtrate was acidified (pH 3) and cooled in an ice bath. The separated solid was collected to give 2-carboxy-4-nitro-1H-benzimidazole (290 mg).

mp : 246-248°C (dec.)

(2) To a mixture of oxalyl chloride (0.063 ml), N,N-dimethylformamide (53 mg) and dichloromethane (3 ml) was added a solution of 2-carboxy-4-nitro-1H-benzimidazole (100 mg) in N,N-dimethylformamide, and the mixture was stirred for 1 hour at ambient temperature. The mixture was dropwise added to 28% aqueous ammonia (5 ml), and the mixture was adjusted pH 3 under ice-cooling. Water was added thereto, the resulting precipitate was collected by filtration to give 2-carbamoyl-4-nitro-1H-benzimidazole (53 mg).

mp : >250°C

(3) A mixture of 2-carbamoyl-4-nitro-1H-benzimidazole (136 mg) and 10% palladium on carbon (15 mg) in methanol (2 ml) was hydrogenated. The catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in 1,2-dichloroethane and to the solution were added triethylamine (81 mg) and 2,6-dichlorobenzoyl chloride (166 mg). The solution was refluxed for 5 hours and cooled. The mixture was washed with 3.6% hydrochloric acid, aqueous saturated sodium bicarbonate and brine, dried over sodium sulfate and evaporated in vacuo. The residue was crystallized from dichloromethane to give 2-carbamoyl-4-(2,6-dichlorobenzoylamino)-1H-benzimidazole (40 mg).

mp : >250°C

(4) 2-Carbamoyl-4-(2,6-dichlorobenzoylamino)-1-(2-oxopropyl)-1H-benzimidazole was obtained according to a similar manner to that of Example 5.

mp : 175-177°C

NMR (DMSO-d_6, δ) : 1.60 (3H, s), 4.33 (1H, d, J=13Hz),

4.53 (1H, d, J=13Hz), 6.35 (1H, m), 7.30-7.80 (5H, m), 8.22 (1H, d, J=8Hz), 9.15 (1H, s), 11.22 (1H, s)

Example 51

(1) A mixture of ethyl 2-amino-3-nitrobenzoate (1.09 g), 10% palladium on carbon (150 mg) in methanol was stirred for 5 hours at ambient temperature under hydrogen atmosphere. Insoluble material was filtered off, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate : n-hexane = 1:2, V/V) to give ethyl 2,3-diaminobenzoate (0.87 g).

mp : 56-58°C

NMR ($CDCl_3$, δ) : 1.38 (3H, t, J=7Hz), 4.33 (2H, q, J=7Hz), 6.60 (1H, t, J=8Hz), 6.85 (1H, d, J=8Hz), 7.49 (1H, d, J=8Hz)

(2) 4-Ethoxycarbonyl-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 3-(1).

mp : 78-80°C

NMR ($CDCl_3$, δ) : 1.48 (3H, t, J=7Hz), 4.50 (2H, q, J=7Hz), 7.45 (1H, t, J=8Hz), 8.08 (1H, d, J=8Hz), 8.11 (1H, d, J=8Hz)

(3) 4-Ethoxycarbonyl-1-(pyridin-4-yl)methyl-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 5.

mp : 125-126°C

NMR ($CDCl_3$, δ) : 1.49 (3H, t, J=7Hz), 4.3 (2H, q, J=7Hz), 5.59 (2H, s), 6.93 (2H, d, J=7Hz), 7.40-7.50 (2H, m), 8.08 (1H, d, J=7Hz), 8.58 (2H, d, J=7Hz)

(4) To a solution of 4-ethoxycarbonyl-1-(pyridin-4-

yl)methyl-2-trifluoromethyl-1H-benzimidazole (282 mg) in methanol (2 ml) and tetrahydrofuran (1 ml) was added 1N sodium hydroxide (1 ml), and the mixture was stirred for 4 hours at ambient temperature. The solvent was removed, and the residue was dissolved in isopropyl alcohol (2 ml). Water was added thereto with stirring, and the resulting precipitate was collected by filtration to give 4-carboxy-1-(pyridin-4-yl)methyl-2-trifluoromethyl-1H-benzimidazole (200 mg).

mp : 178-179°C

NMR (DMSO-d_6, δ) : 5.84 (2H, s), 7.03 (2H, d, J=7Hz), 7.56 (1H, t, J=8Hz), 7.90-8.00 (2H, m), 8.52 (2H, d, J=7Hz)

(5) 4-[N-(2,6-Dichlorophenyl)carbamoyl]-1-(pyridin-4-yl)methyl-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 45.

mp : 187-188°C

NMR ($CDCl_3$, δ) : 5.63 (2H, s), 7.02 (2H, d, J=7Hz), 7.22 (1H, d, J=8Hz), 7.40-7.50 (3H, m), 7.58 (1H, t, J=8Hz), 8.42 (1H, d, J=7Hz), 8.63 (2H, d, J=7Hz), 11.09 (1H, s)

its hydrochloride

mp : 163-244°C

NMR (DMSO-d_6, δ) : 6.10 (2H, s), 7.45 (1H, t, J=8Hz), 7.53 (2H, d, J=7Hz), 7.60-7.80 (3H, m), 8.06 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz), 8.73 (2H, d, J=7Hz), 10.93 (1H, s)

Example 52

(1) 1-tert-Butoxycarbonylmethyl-4-ethoxycarbonyl-2-trifluoromethyl-1H-benzimidazole was obtained by reacting 4-ethoxycarbonyl-2-trifluoromethyl-1H-

benzimidazole with tert-butyl bromcacetate according to a similar manner to that of Example 5.

mp : 122-124°C

NMR ($CDCl_3$, δ) : 1.40 (9H, s), 1.47 (3H, t, J=7Hz), 4.51 (2H, q, J=7Hz), 4.95 (2H, s), 7.51 (1H, t, J=8Hz), 7.57 (1H, d, J=8Hz), 8.08 (1H, d, J=8Hz)

(2) 1-Carboxymethyl-4-ethoxycarbonyl-2-trifluoromethyl-1H-benzimidazole trifluoroacetate was obtained according to a similar manner to that of Example 9.

mp : 118-120°C

NMR ($CDCl-d_3$, δ) : 1.46 (3H, t, J=7Hz), 4.51 (2H, q, J=7Hz), 5.06 (2H, s), 7.51 (1H, t, J=8Hz), 7.59 (1H, d, J=8Hz), 8.07 (1H, d, J=8Hz)

(3) 4-Ethoxycarbonyl-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole was obtained from 1-carboxymethyl-4-ethoxycarbonyl-2-trifluoromethyl-1H-benzimidazole trifluoroacetate and morpholine according to a similar manner to that of Example 14.

mp : 168-169°C

NMR ($CDCl_3$, δ) : 1.47 (3H, t, J=7Hz), 3.0-3.90 (8H, m), 4.51 (2H, q, J=7Hz), 5.12 (2H, s), 7.48 (1H, t, J=8Hz), 7.52 (1H, d, J=8Hz), 8.05 (1H, d, J=8Hz)

(4) 4-Carboxy-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 51-(4).

NMR ($DMSO-d_6$, δ) : 3.40-3.80 (8H, m), 5.55 (2H, s), 7.55 (1H, t, J=8Hz), 7.92 (1H, d, J=8Hz), 8.02 (1H, d, J=8Hz)

(5) 4-[N-(2,6-Dichlorophenyl)carbamoyl]-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner

to that of Example 45.

mp : >250°C

NMR ($CDCl_3$, δ) : 3.40-3.80 (8H, m), 5.65 (2H, s), 7.44 (1H, t, J=8Hz), 7.60-7.80 (3H, m), 8.10-8.20 (2H, m), 10.95 (1H, s)

Example 53

(1) 4-Methyl-2-trifluoromethyl-1H-benzimidazole was obtained by reacting 3-methyl-1,2-phenylenediamine with trifluoroacetic acid according to a similar manner to that of Example 3-(1).

mp : 147-148°C

(2) A suspension of 4-methyl-2-trifluoromethyl-1H-benzimidazole (200 mg) in a mixture of tert-butanol and water was refluxed. The suspension was added potassium permanganate (600 mg) portionwise and the mixture was refluxed for 2 hours. The insoluble solid was filtered off and the filtrate was washed with diethyl ether. The aqueous layer was acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and evaporated in vacuo. The crystalline residue was recrystallized from a mixture of ethyl acetate and hexane to give 4-carboxy-2-trifluoromethyl-1H-benzimidazole (132 mg).

mp : >250°C

NMR (DMSO-d_6, δ) : 7.45 (1H, t, J=8Hz), 8.00-8.20 (2H, m)

(3) A mixture of 4-carboxy-2-trifluoromethyl-1H-benzimidazole (100 mg), chloroacetone (179 mg) and potassium carbonate (179 mg) in N,N-dimethylformamide was stirred at 60°C for 3 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated in

vacuo. The residue was purified by column chromatography on silica gel and the obtained solid was triturated with diisopropyl ether to give 1-(2-oxopropyl)-4-(2-oxopropoxycarbonyl)-2-trifluoromethyl-1H-benzimidazole (79 mg).

mp : 160-162°C

NMR ($CDCl_3$, δ) : 2.29 (3H, s), 2.36 (3H, s), 4.98 (2H, s), 5.13 (2H, s), 7.40-7.60 (2H, m), 8.67 (1H, d, J=8Hz)

(4) To a solution of 1-(2-oxopropyl)-4-(2-oxopropoxycarbonyl)-2-trifluoromethyl-1H-benzimidazole (145 mg) in methanol was added 1N sodium hydroxide solution (1 ml), and the mixture was stirred for 6 hours at ambient temperature. The solvent was removed, and the residue was acidified with hydrochloric acid. The mixture was extracted with ethyl acetate, and the extract was washed with water and brine, dried over magnesium sulfate and concentrated in vacuo to give 4-carboxy-1-(2-oxopropyl)-2-trifluoromethyl-1H-benzimidazole (31.3 mg).

mp : 170-172°C

NMR ($CDCl_3$-CD_3OD, δ) : 2.37 (3H, s), 5.22 (2H, s), 7.54 (1H, t, J=8Hz), 7.61 (1H, d, J=8Hz), 8.23 (1H, d, J=8Hz)

(5) 4-[N-(2,6-Dichlorophenyl)carbamoyl]-1-(2-oxopropyl)-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 45.

mp : 223-225°C

NMR ($CDCl_3$, δ) : 2.35 (3H, s), 5.18 (2H, s), 7.22 (1H, t, J=8Hz), 7.40-7.50 (3H, m), 7.61 (1H, t, J=8Hz), 8.40 (1H, d, J=8Hz), 11.07 (1H, s)

Example 54

(1) A mixture of 3-nitro-1,2-phenylenediamine (0.5 g) and

difluoroacetic acid (314 mg) in 4N hydrochloric acid (9 ml) was heated at 100°C for 42 hours. After cooling, ethyl acetate was added thereto, and insoluble material was filtered off. The separated organic layer was washed with water, dried and concentrated in vacuo to give 2-difluoromethyl-4-nitro-1H-benzimidazole (265 mg).

mp : 136-137°C

NMR ($DMSO-d_6$, δ) : 7.32 (1H, t, J=52Hz), 7.53 (1H, t, J=8Hz), 8.23 (1H, d, J=8Hz), 8.27 (1H, d, J=8Hz)

(2) 4-Amino-2-difluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 3-(2).

mp : 120-124°C

NMR (CD_3OD, δ) : 6.37 (1H, d, J=8Hz), 6.68 (1H, d, J=8Hz), 6.77 (1H, t, J=52Hz), 6.88 (1H, t, J=8Hz)

(3) 4-(2,6-Dichlorobenzoylamino)-2-difluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 1-(2).

mp : 178-180°C

(4) 1-tert-Butoxycarbonylmethyl-4-(2,6-dichlorobenzoylamino)-2-difluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 5.

mp : 196-197°C

NMR ($CDCl_3$, δ) : 1.45 (9H, s), 4.97 (2H, s), 6.87 (1H, t, J=52Hz), 7.13 (1H, d, J=8Hz), 7.30-7.40 (3H, m), 7.46 (1H, t, J=8Hz), 8.52 (1H, d, J=8Hz), 8.54 (1H, br s)

(5) 1-Carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-difluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 9.

mp : >250°C

NMR ($CDCl_3+CD_3OD$, δ) : 5.07 (2H, s), 6.88 (1H, t, J=52Hz), 7.16 (1H, d, J=8Hz), 7.30-7.40 (3H, m), 7.47 (1H, t, J=8Hz), 8.55 (1H, d, J=8Hz)

(6) 4-(2,6-Dichlorobenzoylamino)-2-difluoromethyl-1-(morpholinocarbonyl)methyl-1H-benzimidazole was obtained according to a similar manner to that of Example 14.
mp : 216-217°C
NMR (DMSO-d_6, δ) : 3.40-3.80 (8H, m), 5.44 (2H, s), 7.29 (1H, t, J=53Hz), 7.60-7.30 (5H, m), 8.16 (1H, d, J=8Hz), 11.05 (1H, s)

Example 55

(1) A mixture of 3-nitro-1,2-phenylenediamine (500 mg) and tetramethyl orthocarbonate (533 mg) in acetic acid (5 ml) was stirred at ambient temperature for 2 hours. The mixture was evaporated in vacuo and partitioned between ethyl acetate and aqueous saturated sodium bicarbonate. The organic layer was separated, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diisopropyl ether to give 2-methoxy-4-nitro-1H-benzimidazole (479 mg).
mp : 171-172°C
NMR ($CDCl_3$, δ) : 4.24 (3H, s), 7.26 (1H, t, J=8Hz), 7.82 (1H, d, J=8Hz), 8.00 (1H, d, J=8Hz), 9.69 (1H, m)

(2) 2-Methoxy-4-nitro-1-(2-oxopropyl)-1H-benzimidazole was obtained according to a similar manner to that of Example 5.
mp : 184-187°C
NMR ($CDCl_3$, δ) : 2.24 (3H, s), 4.33 (3H, s), 4.79 (2H, s), 7.18-7.28 (2H, m), 8.03 (1H, d, J=8Hz)

(3) 4-Amino-2-methoxy-1-(2-oxopropyl)-1H-benzimidazole was

obtained according to a similar manner to that of Example 1-(1).

NMR ($CDCl_3$, δ) : 2.11 (3H, s), 3.70 (3H, s), 4.60 (2H, s), 6.43 (1H, d, J=8Hz), 6.51 (1H, d, J=8Hz), 6.95 (1H, t, J=8Hz)

(4) 4-(2,6-Dichlorobenzoylamino)-2-methoxy-1-(2-oxopropyl)-1H-benzimidazole was obtained according to a similar manner to that of Example 1-(2).

mp : 175-177°C

NMR ($CDCl_3$, δ) : 2.20 (3H, s), 4.14 (3H, s), 4.68 (2H, s), 6.81 (1H, d, J=8Hz), 7.20 (1H, t, J=8Hz), 7.30-7.43 (3H, m), 8.35-8.40 (2H, m)

Example 56

(1) A mixture of 3-nitro-1,2-phenylenediamine (2.0 g), carbon disulfide (3.99 g) and potassium hydroxide (807 mg) in a mixture of ethanol (17 ml) and water (3 ml) was refluxed for 5 hours. The reaction mixture was diluted with water (20 ml) and the mixture was adjusted to pH 5 with 1N hydrochloric acid. The separated solid was collected and washed with water to give 2-mercapto-4-nitro-1H-benzimidazole (2.442 g).

mp : >250°C

NMR ($DMSO-d_6$, δ) : 7.30 (1H, t, J=8Hz), 7.51 (1H, d, J=8Hz), 7.94 (1H, d, J=8Hz)

(2) A mixture of 2-mercapto-4-nitro-1H-benzimidazole (400 mg) and 1-bromo-3-chloropropane (341 mg) in a mixture of 1N aqueous sodium hydroxide (2.2 ml) and N,N-dimethylformamide (6 ml) was stirred at 70°C for 1 hours. The mixture was cooled and partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 2-(3-chloropropylthio)-4-nitro-1H-benzimidazole (200 mg).

NMR ($CDCl_3$, δ) : 2.30-2.40 (2H, m), 3.56 (2H, t, J=5Hz), 3.72 (2H, t, J=5Hz), 7.31 (1H, t, J=8Hz), 7.96 (1H, d, J=8Hz), 8.08 (1H, d, J=8Hz), 10.31 (1H, m)

(3) A mixture of 2-(3-chloropropylthio)-4-nitro-1H-benzimidazole (190 mg), potassium carbonate (145 mg) and tetrabutylammonium iodide (10 mg) in N,N-dimethylformamide (3 ml) was stirred at ambient temperature for 3 hours and poured into a mixture of ice and water. The separated solid was collected, dried and purified by column chromatography on silica gel. The obtained oil was crystallized from a mixture of ethanol and water to give 3,4-dihydro-9-nitro-2H-[1,3]thiazino[3,2-a]benzimidazole (110 mg).

mp : 154-155°C

NMR ($CDCl_3$, δ) : 2.49-2.58 (2H, m), 3.27-3.32 (2H, m), 4.27 (2H, t, J=5Hz), 7.24 (1H, t, J=8Hz), 7.50 (1H, d, J=8Hz), 8.08 (1H, d, J=8Hz)

(4) 9-Amino-3,4-dihydro-2H-[1,3]thiazino[3,2-a]benzimidazole was obtained according to a similar manner to that of Example 3-(2).

mp : 160-162°C

NMR ($CDCl_3$, δ) : 2.42-2.51 (2H, m), 3.20-3.26 (2H, m), 4.14 (2H, t, J=5Hz), 4.18-4.30 (2H, m), 6.52 (1H, d, J=8Hz), 6.64 (1H, d, J=8Hz), 7.00 (1H, t, J=8Hz)

(5) 9-(2,6-Dichlorobenzoylamino)-3,4-dihydro-2H-[1,3]thiazino[3,2-a]benzimidazole was obtained according to a similar manner to that of Example 1-(2).

mp : >250°C

NMR (DMSO-d_6, δ) : 2.35-2.46 (2H, m), 3.39-3.45 (2H, m), 4.29-4.37 (2H, m), 7.38 (1H, t, J=8Hz), 7.44-7.60 (4H, m), 7.98 (1H, d, J=8Hz), 11.10 (1H, br s)

Example 57

(1) 2-Methylthio-4-nitro-1H-benzimidazole was obtained by reacting 2-mercapto-4-nitro-1H-benzimidazole with methyl iodide according to a similar manner to that of Example 56-(2).
mp : 163-166°C
NMR ($CDCl_3$, δ) : 2.84 (3H, s), 7.30 (1H, t, J=8Hz), 7.97 (1H,d, J=8Hz), 8.08 (1H, d, J=8Hz), 10.29 (1H, m)

(2) 4-Amino-2-methylthio-1H-benzimidazole was obtained according to a similar manner to that of Example 3-(2).
NMR ($CDCl_3$, δ) : 2.63 (3H, s), 4.12-4.42 (2H, m), 6.51 (1H, d, J=8Hz), 6.76 (1H, d, J=8Hz), 7.00 (1H, t, J=8Hz)

(3) 4-(2,6-Dichlorobenzoylamino)-2-methylthio-1H-benzimidazole was obtained according to a similar manner to that of Example 1-(2).
mp : 238-242°C
NMR (DMSO-d_6, δ) : 2.70 (3H, s), 7.12 (1H, t, J=8Hz), 7.22 (1H, m), 7.42-7.60 (3H, m), 7.90 (1H, m), 10.60 (1H, m), 12.60 (1H, m)

(4) 4-(2,6-Dichlorobenzoylamino)-2-methylthio-1-(2-oxopropyl)-1H-benzimidazole hydrochloride was obtained according to a similar manner to that of Example 5.
mp : 221.5-223°C
NMR (DMSO-d_6, δ) : 2.30 (3H, s), 2.76 (3H, s), 5.30 (2H, s), 7.20-7.34 (2H, m), 7.44-7.60 (3H, m), 8.08 (1H, d, J=8Hz), 10.83 (1H, br s)

Example 58

(1) To a solution of 4-(2,6-dichlorobenzoylamino)-2-methylthio-1H-benzimidazole (100 mg) in dichloromethane (2

ml) was added a solution of hydrogen peroxide in trifluoroacetic acid (1M solution, 0.56 ml) at 4°C. The mixture was stirred at 4°C for 30 minutes, neutralized with aqueous saturated sodium bicarbonate and extracted with a mixture of dichloromethane and ethanol (8:2, V/V). The extract was dried over sodium sulfate and evaporated in vacuo. The residue was crystallized from ethyl acetate to give 4-(2,6-dichlorobenzoylamino)-2-methylsulfonyl-1H-benzimidazole (79 mg).

mp : >250°C

NMR (DMSO-d_6, δ) : 3.08 (3H, s), 7.34 (1H, t, J=8Hz), 7.40-7.64 (4H, m), 8.20 (1H, d, J=8Hz), 10.84 (1H, m)

(2) 4-(2,6-Dichlorobenzoylamino)-2-methylsulfonyl-1-(2-oxopropyl)-1H-benzimidazole was obtained according to a similar manner to that of Example 5.

mp : 232-233°C

NMR ($CDCl_3$, δ) : 2.35 (3H, s), 3.16 (3H, s), 5.26 (1H, d, J=18Hz), 5.54 (1H, d, J=18Hz), 7.04 (1H, d, J=8Hz), 7.30-7.46 (4H, m), 8.48-8.54 (2H, m)

Example 59

(1) A mixture of 2-mercapto-4-nitro-1H-benzimidazole (400 mg) and 2-oxopropyl chloride (248 mg) in ethanol (6 ml) was refluxed for 18 hours. After cooling, the mixture was adjusted pH 8 with saturated sodium bicarbonate solution and extracted with dichloromethane. The extract was washed with brine, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give 4-nitro-2-(2-oxopropylthio)-1H-benzimidazole (388 mg).

mp : 228-231°C (dec.)

NMR ($CDCl_3$, δ) : 2.42 (3H, s), 4.26 (2H, s), 7.31 (1H, t, J=8Hz), 7.92 (1H, d, J=8Hz), 8.07 (1H, d, J=8Hz)

(2) A suspension of 4-nitro-2-(2-oxopropylthio)-1H-benzimidazole (200 mg) in 1N hydrochloric acid (15 ml) was refluxed for 18 hours. The reaction mixture was neutralized with aqueous saturated sodium bicarbonate. The separated solid was collected, dried and purified by column chromatography on silica gel. The obtained oil was crystallized from diisopropyl ether to give 3-methyl-8-nitrothiazolo[3,2-a]benzimidazole (86 mg).

mp : 240-242°C

NMR ($CDCl_6$, δ) : 2.80 (3H, s), 6.56 (1H, s), 7.33 (1H, t, J=8Hz), 8.10 (1H, d, J=8Hz), 8.30 (1H, d, J=8Hz)

(3) A mixture of 3-methyl-8-nitrothiazolo[3,2-a]-benzimidazole (80 mg), reduced iron (96 mg) and acetic acid (412 mg) in dioxane (1.6 ml) and ethanol (116 ml) was refluxed for 30 minutes. After cooling, the mixture was diluted with ethyl acetate, and insoluble material was filtered off. The filtrate was concentrated and the residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was washed with brine, dried and concentrated in vacuo to give 8-amino-3-methylthiazolo[3,2-a]benzimidazole (58 mg).

mp : 155-157°C

NMR ($CDCl_3$, δ) : 2.70 (3H, s), 4.29-4.42 (2H, m), 6.30 (1H, s), 6.75 (1H, d, J=8Hz), 7.05 (1H, t, J=8Hz), 7.20 (1H, d, J=8Hz)

(4) 8-(2,6-Dichlorobenzoylamino)-3-methylthiazolo[3,2-a]-benzimidazole was obtained according to a similar manner to that of Example 1-(2).

mp : >250°C

NMR (DMSO-d_6, δ) : 2.78 (3H, s), 7.03 (1H, s), 7.36 (1H, t, J=8Hz), 7.48-7.60 (3H, m), 7.86 (1H, d, J=8Hz), 8.09 (1H, d, J=8Hz), 11.10 (1H, br s)

Example 60

(1) A mixture of 3-nitro-1,2-phenylenediamine (400 mg) and methyl isothiocyanate (420 mg) in ethanol (4 ml) was stirred at 50°C for 3 hours. To the reaction mixture was added water and the separated solid was collected to give 1-(2-amino-3-nitrophenyl)-3-methylthiourea (441 mg).

mp : >250°C

NMR ($CDCl_3$, δ) : 3.14 (3H, d, J=3Hz), 5.74 (1H, m), 6.32-6.52 (2H, m), 6.76 (1H, t, J=8Hz), 7.26 (1H, m), 7.44 (1H, d, J=8Hz), 8.22 (1H, d, J=8Hz)

(2) A mixture of 1-(2-amino-3-nitrophenyl)-3-methylthiourea (340 mg) and iodomethane (639 mg) in acetonitrile (7 ml) was stirred at 50°C for 8 hours and refluxed for 18 hours. The reaction mixture was cooled, evaporated in vacuo and diluted with dichloromethane. The solution was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtain oil was crystallized from a mixture of ethyl acetate and hexane (1:4, V/V) to give 2-methylamino-4-nitro-1H-benzimidazole (103 mg).

mp : 250-252°C

NMR ($CDCl_3$:CD_3OD = 20:1, δ) : 3.10 (3H, s), 7.11 (1H, t, J=8Hz), 7.61 (1H, m), 7.80 (1H, d, J=8Hz)

(3) 2-Methylamino-4-nitro-1-(2-oxopropyl)-1H-benzimidazole was obtained according to a similar manner to that of Example 5.

mp : 198-200°C

NMR (DMSO-d_6, δ) : 2.22 (3H, s), 2.98 (3H, d, J=5Hz), 5.05 (2H, s), 6.98 (1H, t, J=8Hz), 7.23 (1H, m), 7.43 (1H, d, J=8Hz), 7.75 (1H, d, J=8Hz)

(4) A mixture of 2-methylamino-4-nitro-1-(2-oxopropyl)-1H-benzimidazole (40 mg) and conc. hydrochloric acid (0.13 ml)

in ethanol (1 ml) was stirred at 60°C for 1 hour. To the mixture was added iron powder (36 mg) and the mixture was refluxed for 3 hours. The reaction mixture was neutralized with aqueous sodium bicarbonate and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was treated with methanolic hydrogen chloride to give 8-amino-1,2-dimethyl-1H-imidazo[1,2-a]benzimidazole hydrochloride (38 mg).

NMR ($CDCl_3$-CD_3OD, 20:1, δ) : 2.47 (3H, s), 3.91 (3H, s), 7.22 (1H, d, J=8Hz), 7.35 (1H, t, J=8Hz), 7.47 (1H, d, J=8Hz), 7.54 (1H, s)

(5) 8-(2,6-Dichlorobenzoylamino)-1,2-dimethyl-1H-imidazo[1,2-a]benzimidazole hydrochloride was obtained according to a similar manner to that of Example 1-(2).

mp : >250°C

NMR (DMSO-d_6, δ) : 2.40 (3H, s), 3.76 (3H, s), 7.42 (1H, t, J=8Hz), 7.52-7.66 (3H, m), 7.82 (1H, d, J=8Hz), 7.94 (1H, s), 8.18 (1H, d, J=8Hz), 11.02 (1H, br s)

Example 61

(1) A mixture of 4-amino-1H-benzimidazole (260 mg), 2,6-dichlorobenzoyl chloride (436 mg) and triethylamine (300 mg) in dichloromethane (5 ml) was stirred at ambient temperature for 2 hours. The reaction mixture was evaporated in vacuo and the residue was purified by column chromatography on silica gel to give 4-amino-1-(2,6-dichlorobenzoyl)-1H-benzimidazole (251 mg).

mp : 141-149°C

NMR ($CDCl_3$, δ) : 4.38-4.48 (2H, m), 6.73 (1H, d, J=8Hz), 7.30 (1H, t, J=8Hz), 7.47-7.51 (3H, m), 7.57 (1H, br s), 7.80 (1H, d, J=8Hz)

(2) 1-(2,6-Dichlorobenzoyl)-4-(2,6-dichlorobenzoylamino)-1H-benzimidazole was obtained according to a similar manner to that of Example 1-(2).
NMR ($CDCl_3$, δ) : 6.30-7.42 (3H, m), 7.48-7.66 (5H, m), 8.22 (1H, m), 8.56 (1H, m), 8.64 (1H, m)

(3) A mixture of 1-(2,6-dichlorobenzoyl)-4-(2,6-dichlorobenzoylamino)-1H-benzimidazole (380 mg) and 1N aqueous sodium hydroxide solution (1 ml) in ethanol (4 ml) was stirred at ambient temperature for 30 minutes and at 60°C for 1 hour. The mixture was neutralized with 1N hydrochloric acid and extracted with dichloromethane. The extract was dried over sodium sulfate and evaporated in vacuo to give 4-(2,6-dichlorobenzoylamino)-1H-benzimidazole (111 mg).
mp : >250°C
NMR ($CDCl_3$-CD_3OD, δ) : 7.26-7.44 (5H, m), 7.94 (1H, m), 8.44 (1H, m)

(4) 4-(2,6-Dichlorobenzoylamino)-1-(2-oxopropyl)-1H-benzimidazole hydrochloride was obtained according to a similar manner to that of Example 5.
mp : 227-229°C
NMR (DMSO-d_6, δ) : 2.32 (3H, s), 5.54 (2H, s), 7.46-7.64 (5H, m), 8.04 (1H, d, J=8Hz), 9.00 (1H, m), 11.28 (1H, br s)

Example 62

(1) 1-(tert-Butoxycarbonyl)methyl-2-tert-butoxycarbonyl-methoxycarbonyl-4-nitro-1H-benzimidazole was obtained by reacting 2-carboxy-4-nitro-1H-benzimidazole with tert-butyl bromoacetate according to a similar manner to that of Example 5.
mp : 149-151°C
NMR ($CDCl_3$, δ) : 1.44 (9H, s), 1.49 (9H, s), 4.36 (2H, s), 5.33 (2H, s), 7.57 (1H, t, J=8Hz), 7.72 (1H, d,

J=8Hz), 8.25 (1H, d, J=8Hz)

(2) To a mixture of conc. aqueous ammonia (5 ml), N,N-dimethylformamide (15 ml) and tetrahydrofuran (5 ml) was added a solution of 1-(tert-butoxycarbonyl)methyl-2-tert-butoxycarbonylmethoxycarbonyl-4-nitro-1H-benzimidazole (1.4 g) in N,N-dimethylformamide (5 ml) at 0°C, and the mixture was stirred for 30 minutes at the same temperature. The mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and concentrated in vacuo to give 1-(tert-butoxycarbonyl)methyl-2-carbamoyl-4-nitro-1H-benzimidazole (939 mg).

mp : 201-202°C

NMR ($CDCl_3$-CD_3OD, δ) : 1.47 (9H, s), 5.44 (2H, s), 7.55 (1H, t, J=8Hz), 7.73 (1H, d, J=8Hz), 8.28 (1H, d, J=8Hz)

(3) To a solution of 1-(tert-butoxycarbonyl)methyl-2-carbamoyl-4-nitro-1H-benzimidazole (500 mg) in N,N-dimethylformamide (5 ml) was dropwise added thionyl chloride (223 mg), and the mixture was stirred for 3 hours at ambient temperature. The mixture was poured into saturated sodium bicarbonate solution and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate : n-hexane = 2:3, V/V) to give 1-(tert-butoxycarbonyl)methyl-2-cyano-4-nitro-1H-benzimidazole (349 mg).

mp : 136-138°C

NMR ($CDCl_3$, δ) : 1.48 (9H, s), 7.65 (1H, t, J=8Hz), 7.72 (1H, d, J=8Hz), 8.32 (1H, d, J=8Hz)

(4) 4-Amino-1-(tert-butoxycarbonyl)methyl-2-cyano-1H-benzimidazole was obtained according to a similar manner

to that of Example 1-(1).
mp : 160-162°C
NMR ($CDCl_3$, δ) : 1.47 (9H, s), 4.52 (2H, br s), 4.40 (2H, s), 6.59 (1H, d, J=8Hz), 6.66 (1H, d, J=8Hz), 7.26 (1H, t, J=8Hz)

(5) 1-(tert-Butoxycarbonyl)methyl-2-cyano-4-(2,6-dichlorobenzoylamino)-1H-benzimidazole was obtained according to a similar manner to that of Example 1-(2).
mp : 187-189°C
NMR ($CDCl_3$, δ) : 1.49 (9H, s), 4.97 (2H, s), 7.23 (1H, d, J=8Hz), 7.30-7.50 (2H, m), 7.55 (1H, t, J=8Hz), 8.50-8.60 (2H, m)

(6) 1-Carboxymethyl-2-cyano-4-(2,6-dichlorobenzoylamino)-1H-benzimidazole was obtained according to a similar manner to that of Example 9.
mp : 218-221°C
NMR (DMSO-d_6, δ) : 5.40 (2H, s), 7.40-7.65 (5H, m), 8.77 (1H, d, J=8Hz)

Example 63

The following compounds were obtained according to a similar manner to that of Example 14.

(1) 2-Cyano-4-(2,6-dichlorobenzoylamino)-1-(morpholinocarbonyl)methyl-1H-benzimidazole (from 1-carboxymethyl-2-cyano-4-(2,6-dichlorobenzoylamino)-1H-benzimiazole and morpholine)
mp : >250°C
NMR (DMSO-d_6, δ) : 3.49 (2H, m), 3.50-3.70 (4H, m), 3.73 (2H, m), 5.60 (2H, s), 7.40-7.60 (5H, m), 8.25 (1H, m)

(2) 2-Cyano-4-(2,6-dichlorobenzoylamino)-1-[N-(5-

trifluoromethyl-1,3,4-thiadiazol-2-yl)carbamoylmethyl]-1H-benzimidazole
(from 1-carboxymethyl-2-cyano-4-(2,6-dichlorobenzoylamino)-1H-benzimidazole and 2-amino-5-trifluoromethyl-1,3,4-thiadiazole)
mp : >250°C
NMR (DMSO-d_6, δ) : 5.65 (2H, s), 7.40-7.60 (5H, m), 8.27 (1H, m)

(3) 2-Cyano-4-(2,6-dichlorobenzoylamino)-1-[N-(2-hydroxyethyl)carbamoylmethyl]-1H-benzimiazole
(from 1-carboxymethyl-2-cyano-4-(2,6-dichlorobenzoylamino)-1H-benzimidazole and (2-hydroxyethyl)amine)
mp : 222-224°C
NMR (DMSO-d_6, δ) : 3.19 (2H, m), 3.45 (2H, m), 4.78 (1H, t, J=6Hz), 5.17 (2H, s), 7.40-7.60 (5H, m), 8.25 (1H, d, J=8Hz), 8.56 (1H, t, J=6Hz)

(4) 2-Cyano-4-(2,6-dichlorobenzoylamino)-1-[N-(pyridin-2-ylmethyl)carbamoylmethyl]-1H-benzimidazole hydrochloride
(from 1-carboxymethyl-2-cyano-4-(2,6-dichlorobenzoylamino)-1H-benzimidazole and 2-aminomethylpyridine)
mp : 215-237°C (dec.)
NMR (DMSO-d_6, δ) : 4.63 (2H, d, J=6Hz), 5.37 (2H, s), 7.40-7.80 (7H, m), 8.15-8.30 (2H, m), 8.72 (1H, d, J=5Hz), 9.38 (1H, t, J=6Hz)

(5) 2-Cyano-4-(2,6-dichlorobenzoylamino)-1-[N-(2-methoxyethyl)carbamoylmethyl]-1H-benzimidazole
(from 1-carboxymethyl-2-cyano-4-(2,6-dichlorobenzoylamino)-1H-benzimidazole and (2-methoxyethyl)amine)
mp : 196°C

NMR (DMSO-d_6, δ) : 3.28 (3H, s), 3.28-3.35 (2H, m), 3.39 (2H, t, J=5Hz), 5.17 (2H, s), 7.40-7.60 (5H, m), 8.26 (1H, d, J=8Hz), 8.65 (1H, t, J=5Hz)

(6) 2-Cyano-4-(2,6-dichlorobenzoylamino)-1-(N-cyclopentylcarbamoylmethyl)-1H-benzimidazole
(from 1-carboxymethyl-2-cyano-4-(2,6-dichlorobenzoylamino)-1H-benzimidazole and cyclopentylamine)
mp : 217-219°C
NMR (DMSO-d_6, δ) : 1.30-1.90 (8H, m), 4.03 (1H, m), 5.11 (2H, s), 7.40-7.60 (5H, m), 8.26 (1H, d, J=8Hz), 8.52 (1H, d, J=7Hz)

Example 64

The following compounds were obtained according to a similar manner to that of Example 5.

(1) 4-(2,6-Dichlorobenzoylamino)-1-methoxymethyl-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and chloromethyl methyl ether)
mp : 153-155°C
NMR ($CDCl_3$, δ) : 3.36 (3H, s), 5.65 (2H, s), 7.30-7.43 (4H, m), 7.52 (1H, t, J=8Hz), 8.58 (1H, d, J=8Hz), 8.61 (1H, s)

(2) 4-(2,6-Dichlorobenzoylamino)-1-allyl-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and allyl bromide)
mp : 120-122°C
NMR ($CDCl_3$, δ) : 4.44 (2H, d, J=5Hz), 5.17 (1H, d, J=16Hz), 5.31 (1H, d, J=10Hz), 5.98 (1H, m), 7.21 (1H, d, J=8Hz), 7.31-7.43 (3H, m), 7.50 (1H, t, J=8Hz), 8.59 (1H, d, J=8Hz), 8.65 (1H, br s)

(3) 4-(2,6-Dichlorobenzoylamino)-1-(3,4-methylenedioxybenzyl)-2-trifluoromethyl-1H-benzimidazole
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 3,4-(methylenedioxy)benzyl chloride)
mp : 97-101°C
NMR ($CDCl_3$, δ) : 5.42 (2H, s), 5.94 (2H, s), 6.58 (1H, s), 6.64 (1H, d, J=8Hz), 6.76 (1H, d, J=8Hz), 7.09 (1H, d, J=8Hz), 7.30-7.45 (4H, m), 8.55 (1H, d, J=8Hz), 8.63 (1H, br s)

(4) 4-(2,6-Dichlorobenzoylamino)-1-(5-methylimidazol-4-yl)methyl-2-trifluoromethyl-1H-benzimidazole hydrochloride
(from 4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and 1-(p-toluenesulfonyl)-4-chloromethyl-5-methylimidazole)
mp : 212-216°C
NMR (DMSO-d_6, δ) : 2.26 (3H, s), 5.80 (2H, s), 7.38 (1H, d, J=8Hz), 7.47 (1H, d, J=8Hz), 7.50-7.57 (3H, m), 8.26 (1H, d, J=8Hz), 9.02 (1H, s)

(5) 4-[N-(2,6-Dichlorophenyl)carbamoyl]-1-(2-methylimidazol-3-yl)methyl-2-trifluoromethyl-1H-benzimidazole
(from 4-[N-(2,6-dichlorophenyl)carbamoyl]-2-trifluoromethyl-1H-benzimidazole and 1-(p-toluenesulfonyl)-4-chloromethyl-5-methylimidazole)
mp : 203-204°C
NMR (DMSO-d_6, δ) : 2.30 (3H, s), 5.58 (2H, s), 7.51 (1H, s), 7.53 (1H, t, J=8Hz), 7.63 (2H, d, J=8Hz), 7.66 (1H, t, J=8Hz), 8.11 (1H, d, J=8Hz), 8.15 (1H, d, J=8Hz)

Example 65

(1) 1-tert-Butoxycarbonylmethyl-4-nitro-2-trifluoromethyl-1H-benzimidazole was obtained by reacting 4-nitro-2-

trifluoromethyl-1H-benzimidazole with tert-butyl bromoacetate according to a similar manner to that of Example 5.

mp : 163-168°C

NMR ($CDCl_3$, δ) : 1.42 (9H, s), 5.01 (2H, s), 7.60 (1H, t, J=8Hz), 7.71 (1H, d, J=8Hz), 8.27 (1H, d, J=8Hz)

(2) 1-Carboxymethyl-4-nitro-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 9.

mp : 223-224°C

NMR (DMSO-d_6, δ) : 5.43 (2H, s), 7.72 (1H, t, J=8Hz), 8.28 (1H, d, J=8Hz), 8.39 (1H, d, J=8Hz)

(3) 1-(Morpholinocarbonyl)methyl-4-nitro-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 14

mp : 212-214°C

NMR ($CDCl_3$, δ) : 3.58-3.69 (4H, m), 3.69-3.86 (4H, m), 5.17 (2H, s), 7.56 (1H, t, J=8Hz), 7.68 (1H, d, J=8Hz), 8.23 (1H, d, J=8Hz)

(4) 4-Amino-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 59-(3).

mp : 202-205°C

NMR ($CDCl_3$, δ) : 3.52-3.69 (4H, m), 3.69-3.81 (4H, m), 4.47 (2H, br s), 5.00 (2H, s), 6.58 (1H, d, J=8Hz), 6.52 (1H, d, J=8Hz), 7.20 (1H, t, J=8Hz)

(5) A mixture of 2,6-dichloro-3-formylbenzoic acid (63 mg) and thionyl chloride (725 mg) in toluene (1 ml) was refluxed for 1.5 hours. After concentration of the mixture, the residue was dissolved in dichloromethane (1 ml) and to the

solution was added 4-amino-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole (80 mg) and triethylamine (57 mg) with ice cooling. After stirring for 3 hours at ambient temperature, the resulting mixture was purified by column chromatography on silica gel (1% methanol in dichloromethane). The obtained solid was triturated with diethyl ether to give 4-(2,6-dichloro-3-formylbenzoylamino)-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole (56 mg).

mp : 189-192°C

NMR ($CDCl_3$, δ) : 3.57-3.70 (4H, m), 3.70-3.85 (4H, m), 5.11 (2H, s), 7.20-7.29 (2H, m), 7.44-7.51 (2H, m), 8.48 (1H, d, J=8Hz), 9.65 (1H, s)

(6) A mixture of 4-(2,6-dichloro-3-formylbenzoylamino)-1-morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole (100 mg) and sodium borohydride (11 mg) in ethanol (2 ml) and tetrahydrofuran (1 ml) was stirred for 6 hours at ambient temperature. To the resulting mixture was added water and the separated solid was collected to give 4-(2,6-dichloro-3-hydroxymethylbenzoylamino)-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole (87 mg).

mp : >260°C

NMR (DMSO-d_6, δ) : 3.41-3.49 (2H, m), 3.55-3.67 (4H, m), 3.67-3.73 (2H, m), 4.59 (2H, d, J=6Hz), 5.50 (2H, s), 5.60 (1H, d, J=6Hz), 7.47 (1H, t, J=8Hz), 7.50 (1H, d, J=8Hz), 7.53 (1H, d, J=8Hz), 7.61 (1H, d, J=8Hz), 8.22 (1H, d, J=8Hz)

(7) A mixture of 4-(2,6-dichloro-3-formylbenzoylamino)-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole (100 mg) and ethyl (triphenylphosphoranylidene)acetate (79 mg) was stirred for 1.5 hour at ambient temperature. The resulting mixture was purified by column chromatography on silica gel (0.5%-1% methanol in dichloromethane). The

obtained oil was crystallized from a mixture of ethanol and water to give (E)-4-[2,6-dichloro-3-(2-ethoxycarbonylethenyl)benzoylamino]-1-(morpholinocarbonyl)-methyl-2-trifluoromethyl-1H-benzimidazole (96 mg).

mp : 258-260°C

NMR ($CDCl_3$, δ) : 1.24 (0.75H, t, J=7Hz), 1.37 (2.25H, t, J=7Hz), 3.57-3.70 (4H, m), 3.70-3.86 (4H, m), 4.19 (0.5H, q, J=7Hz), 4.30 (1.5H, q, J=7Hz), 5.10 (2H, s), 6.17 (0.25H, d, J=15Hz), 6.48 (0.75H, d, J=15Hz), 7.05-7.13 (1H, m), 7.36-7.53 (2H, m), 7.60 (0.25H, d, J=8Hz), 8.02 (0.75H, d, J=15Hz), 7.54-8.69 (2.25H, m)

Example 66

(1) A mixture of 4-ethoxycarbonyl-2-trifluoromethyl-1H-benzimidazole (258 mg), 2-benzyloxyethyl bromide (301 mg), potassium iodide (33 mg) and potassium carbonate (345 mg) in N,N-dimethylformamide (2 ml) was stirred for 14 hours at 70°C. The mixture was partitioned between ethyl acetate and 3% aqueous sodium bicarbonate. The separated organic phase was concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate/n-hexane = 1/4-1/3) to give 4-ethoxycarbonyl-1-(2-benzyloxyethyl)-2-trifluoromethyl-1H-benzimidazole (333 mg) as oil.

NMR ($CDCl_3$, δ) : 1.48 (3H, t, J=7Hz), 3.82 (2H, t, J=6Hz), 4.41 (2H, s), 4.51 (2H, q, J=7Hz), 4.56 (2H, t, J=6Hz), 7.07-7.12 (2H, m), 7.22-7.29 (3H, m), 7.44 (1H, t, J=8Hz), 7.79 (1H, d, J=8Hz), 8.04 (1H, d, J=8Hz)

(2) A mixture of 4-ethoxycarbonyl-1-(2-benzyloxyethyl)-2-trifluoromethyl-1H-benzimidazole (325 mg) and 1N aqueous sodium hydroxide (1.5 ml) in ethanol (1.5 ml) was stirred for 8 hours at ambient temperature. The mixture was acidified with 1N aqueous hydrochlolic acid and extracted with ethyl

acetate. The organic phase was dried over sodium sulfate and evaporated in vacuo. The residue was crystallized from a mixture of diethyl ether and ethanol to give 4-carboxy-1-(2-benzyloxyethyl)-2-trifluoromethyl-1H-benzimidazole (174 mg).

mp : 117-118°C

NMR (DMSO-d_6, δ) : 3.80 (2H, t, J=6Hz), 4.40 (2H, s), 4.69 (2H, t, J=6Hz), 7.01-7.09 (2H, m), 7.18-7.24 (3H, m), 7.52 (1H, t, J=8Hz), 7.91 (1H, d, J=8Hz), 8.07 (1H, d, J=8Hz)

(3) A mixture of 4-carboxy-1-(2-benzyloxyethyl)-2-trifluoromethyl-1H-benzimidazole (260 mg), oxalyl chloride (136 mg) and N,N-dimethylformamide (one drop) in dichloromethane (3 ml) was stirred for 1 hour at ambient temperature. The mixture was concentrated and the residue was dissolved in dichloromethane (3 ml). To this solution was added 2,6-dichloroaniline (173 mg) and triethylamine (144 mg) with ice cooling. After stirring for 2 hours with ice cooling, the mixture was stirred for 1 hour at ambient temperature. The resulting mixture was washed successively with water and brine, dried over sodium sulfate and concentrated. The obtained residue was purified by column chromatography on silica gel (ethyl acetate/n-hexane = 1/5-1/4) to give 4-[N-(2,6-dichlorophenyl)carbamoyl]-1-(2-benzyloxyethyl)-2-trifluoromethyl-1H-benzimidazole (298 mg) as solid after crystallization from diethyl ether.

mp : 143-144°C

NMR ($CDCl_3$, δ) : 3.87 (2H, t, J=6Hz), 4.45 (2H, s), 4.59 (2H, t, J=6Hz), 7.04-7.11 (2H, m), 7.19-7.29 (4H, m), 7.45 (2H, d, J=8Hz), 7.56 (1H, t, J=8Hz), 7.79 (1H, d, J=8Hz), 8.38 (1H, d, J=8Hz)

(4) A mixture of 4-[N-(2,6-dichlorophenyl)carbamoyl]-1-(2-benzyloxyethyl)-2-trifluoromethyl-1H-benzimidazole (100 mg) and 10% palladium on activated carbon (15 mg) in methanol

(0.5 ml) and dioxane (1 ml) was stirred under a hydrogen atmosphere (1 atm) for 1 hour at ambient temperature. The catalyst was removed by filtration and the filtrate was evaporated in vacuo to give 4-[N-(2,6-dichlorophenyl)-carbamoyl]-1-(2-hydroxyethyl)-2-trifluoromethyl-1H-benzimidazole (69 mg) as solid after crystallization from diethyl ether.

mp : 234-238°C

NMR ($CDCl_3$, δ) : 1.93 (1H, t, J=6Hz), 4.10 (2H, q, J=6Hz), 4.59 (2H, t, J=6Hz), 7.21 (1H, t, J=8Hz), 7.43 (2H, d, J=8Hz), 7.60 (1H, t, J=8Hz), 7.84 (1H, d, J=8Hz), 8.33 (1H, d, J=8Hz)

(5) To a mixture of 4-[N-(2,6-dichlorophenyl)carbamoyl]-1-(2-hydroxyethyl)-2-trifluoromethyl-1H-benzimidazole (148 mg) and N-bromosuccinimide (82 mg) in dichloromethane (2 ml) was added triphenylphosphine (121 mg) in dichloromethane (0.5 ml) with ice ccoling. After stirring for 1 hour, the resulting solution was purified by column chromatography on silica gel (ethyl acetate/n-hexane = 1/3). The obtained oil was crystallized from a mixture of diethyl ether and n-hexane to give 4-[N-(2,6-dichlorophenyl)carbamoyl]-1-(2-bromoethyl)-2-trifluoromethyl-1H-benzimidazole (123 mg) as solid.

mp : 170-171°C

NMR ($CDCl_3$, δ) : 3.71 (2H, t, J=7Hz), 4.80 (2H, t, J=7Hz), 7.22 (1H, t, J=8Hz), 7.44 (2H, d, J=8Hz), 7.66 (1H, t, J=8Hz), 7.78 (1H, d, J=8Hz), 8.42 (1H, d, J=8Hz)

(6) A mixture of 4-[N-(2,6-dichlorophenyl)carbamoyl]-1-(2-bromoethyl)-2-trifluoromethyl-1H-benzimidazole (115 mg), 2-mercaptoimidazole (31 mg) and potassium carbonate (50 mg) was stirred for 3 hours at ambient temperature. To the resulting mixture was added a mixture of water and ethanol (2/1) and the separated solid was collected to give 4-[N-(2,6-

dichlorophenyl)carbamoyl]-1-[2-(2-imidazolylthio)ethyl]-2-trifluoromethyl-1H-benzimidazole (110 mg).

mp : 202-204°C

NMR (DMSO-d_6, δ) : 3.49 (2H, t, J=7Hz), 4.82 (2H, t, J=7Hz), 7.11 (2H, s), 7.43 (1H, t, J=8Hz), 7.63 (2H, d, J=8Hz), 7.70 (1H, d, J=8Hz), 8.12 (1H, d, J=8Hz), 8.27 (1H, d, J=8Hz)

(7) A mixture of 4-[N-(2,6-dichlorophenyl)carbamoyl]-1-[2-(2-imidazolylthio)ethyl]-2-trifluoromethyl-1H-benzimidazole (100 mg) in methanol was treated with excess of 10% hydrogen chloride in methanol. The resulting solution was concentrated and the obtained oil was crystallized from diethyl ether to give 4-[N-(2,6-dichlorophenyl)carbamoyl]-1-[2-(2-imidazolylthio)ethyl]-2-trifluoromethyl-1H-benzimidazole hydrochloride (100 mg).

mp : 156°C

NMR (DMSO-d_6, δ) : 3.73 (2H, t, J=7Hz), 4.70 (2H, t, J=7Hz), 7.43 (1H, t, J=8Hz), 7.60 (2H, s), 7.64 (2H, d, J=8Hz), 7.70 (1H, t, J=8Hz), 8.13 (1H, d, J=8Hz), 8.21 (1H, d, J=8Hz)

Example 67

(1) To a solution of 4-(2,6-dichlorobenzoylamino)-1-(2-hydroxyethyl)-2-trifluoromethyl-1H-benzimidazole (126 mg) in dichloromethane was added triphenylphosphine (119 mg) and carbon tetrabromide (150 mg), and the mixture was stirred at ambient temperature overnight. The resulting mixture was purified by column chromatography on silica gel and the obtained oil was crystallized from hexane to give 1-(2-bromoethyl)-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (99 mg).

mp : 175-176°C

NMR ($CDCl_3$, δ) : 3.67 (2H, t, J=8Hz), 4.70 (2H, t, J=8Hz), 7.28 (1H, d, J=8Hz), 7.30-7.42 (3H, m),

7.52 (1H, t, J=8Hz), 8.60 (1H, d, J=8Hz), 8.60 (1H, s)

(2) 4-(2,6-Dichlorobenzoylamino)-1-[2-(imidazol-2-ylthio)-ethyl]-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 66-(6).
NMR (DMSO-d_6, δ) : 3.42 (2H, t, J=8Hz), 4.70 (2H, t, J=8Hz), 7.13 (2H, s), 7.40-7.55 (4H, m), 7.61 (1H, d, J=8Hz), 8.22 (1H, d, J=8Hz)

(3) 4-(2,6-Dichlorobenzoylamino)-1-[2-(imidazol-2-ylthio)ethyl]-2-trifluoromethyl-1H-benzimidazole hydrochloride was obtained from a similar manner to that of Example 66-(7).
mp : 158-168°C
NMR (DMSO-d_6, δ) : 3.73 (2H, t, J=8Hz), 4.68 (2H, t, J=2Hz), 7.40-7.62 (5H, m), 7.65 (2H, s), 8.22 (1H, d, J=8Hz)

Example 68

The following compounds were obtained according to a similar manner to that of Example 66-(6).

(1) 4-[N-(2,6-Dichlorophenyl)carbamoyl]-1-[2-(2-pyridylthio)ethyl]-2-trifluoromethyl-1H-benzimidazole
mp : 176-178°C
NMR ($CDCl_3$, δ) : 3.55-3.61 (2H, m), 4.64 (2H, m), 7.08 (1H, t, J=8Hz), 7.19 (1H, d, J=8Hz), 7.31-7.42 (3H, m), 7.49-7.57 (2H, m), 7.67 (1H, d, J=8Hz), 8.52-8.60 (3H, m)

(2) 4-(2,6-Dichlorobenzoylamino)-1-[2-(5-methyl-1,3,4-thiadiazol-2-ylthio)ethyl]-2-trifluoromethyl-1H-benzimidazole
mp : 206-208°C

NMR ($CDCl_3$, δ) : 2.78 (3H, s), 3.70 (2H, t, J=7Hz), 4.33 (2H, t, J=7Hz), 7.29-7.42 (3H, m), 7.53 (1H, t, J=8Hz), 7.63 (1H, d, J=8Hz), 8.67 (1H, d, J=8Hz), 8.69 (1H, br s)

(3) 4-(2,6-Dichlorobenzoylamino)-1-[2-(1H-imidazo[4,5-b]-pyridin-2-ylthio)ethyl]-2-trifluoromethyl-1H-benzimidazole

mp : >250°C

NMR (DMSO-d_6, δ) : 3.27 (2H, t, J=7Hz), 4.34 (2H, t, J=7Hz), 7.18 (1H, dd, J=5, 8Hz), 7.42-7.58 (4H, m), 7.87 (2H, d, J=8Hz), 8.23 (2H, d, J=8Hz)

its hydrochloride

mp : 246-254°C

NMR (DMSO-d_6, δ) : 3.83 (2H, t, J=7Hz), 4.84 (2H, t, J=7Hz), 7.40-7.60 (5H, m), 7.82 (1H, d, J=8Hz), 8.22 (2H, d, J=8Hz), 8.42 (1H, d, J=8Hz)

Example 69

(1) A mixture of 2-(2,4-dichlorophenyl)ethanol (5.12 g), tert-butylchlorodiphenylsilane (7.37 g) and imidazole (2.37 g) in N,N-dimethylformamide (15 ml) was stirred for 66 hours at ambient temperature. The resulting mixture was partitioned between diethyl ether and water. The organic phase was concentrated in vacuo to give 2-(2,4-dichlorophenyl)-1-(tert-butyldiphenylsilyloxy)ethane (11.8 g) as oil.

NMR ($CDCl_3$, δ) : 1.01 (9H, s), 2.96 (2H, t, J=6Hz), 3.84 (2H, t, J=6Hz), 7.15 (2H, s), 7.29 (1H, s), 7.29-7.43 (6H, m), 7.56 (4H, d, J=8Hz)

(2) To a solution of 2-(2,4-dichlorophenyl)-1-tert-butyldiphenylsilyloxy)ethane (11.8 g) in dry tetrahydrofuran (40 ml) was added 15% n-butyllithium in n-hexane (20.1 ml)

dropwise in a dry ice-acetone bath while the resulting solution was maintained at -55-60°C. After the addition was complete, the mixture was stirred for 1 hour under the same condition and then stirred for 30 minutes at -50°C. The resulting solution was poured into a powder of dry ice (67 g) and the mixture was stood for 3 hours at ambient temperature. The resulting mixture was partitioned between diethyl ether (30 ml) and 2N aqueous sodium hydroxide (70 ml). The separated ether layer was concentrated in vacuo to give 2,6-dichloro-3-[2-(tert-butyldiphenylsilyloxy)ethyl]benzoic acid (11.3 g) as amorphous.

NMR ($CDCl_3$, δ) : 0.99 (9H, s), 2.80 (2H, t, J=6Hz), 3.73 (2H, t, J=6Hz), 6.88 (2H, s), 7.22-7.34 (6H, m), 7.51-7.59 (4H, m)

(3) 4-{2,6-Dichloro-3-[2-(tert-butyldiphenylsilyloxy)ethyl]-benzoylamino}-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole was obtained from 2,6-dichloro-3-[2-(tert-butyldiphenylsilyloxy)ethyl]benzoic acid and 4-amino-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole according to a similar manner to that of Example 66-(3).

NMR ($CDCl_3$, δ) : 1.05 (9H, s), 3.00 (2H, t, J=6Hz), 3.57-3.70 (4H, m), 3.70-3.86 (4H, m), 3.91 (1H, t, J=6Hz), 5.10 (2H, s), 7.10 (1H d, J=8Hz), 7.27 (2H, s), 7.35-7.51 (6H, m), 7.61 (4H, d, J=8Hz), 8.51-8.60 (2H, m)

(4) A mixture of 4-{2,6-dichloro-3-[2-(tert-butyldiphenylsilyloxy)ethyl]benzoylamino}-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole (595 mg) and tetrabutylammonium fluoride (0.9 ml, 1M in tetrahydrofuran) was stirred for 3 hours at ambient temperature. The resulting mixture was concentrated in vacuo and the obtained oil was crystallized from a mixture of ethyl acetate and diethyl ether to give a solid. The crude product

was purified by washing with hot ethanol to give 4-[2,6-dichloro-3-(2-hydroxyethyl)benzoylamino]-1-(morpholino-carbonyl)methyl-2-trifluoromethyl-1H-benzimidazole (186 mg).

mp : 240-241°C

NMR ($CDCl_3$, δ) : 3.03 (2H, t, J=7Hz), 3.58-3.70 (4H, m), 3.70-3.91 (6H, m), 5.10 (2H, s), 7.11 (1H, d, J=8Hz), 7.33 (2H, s), 7.50 (1H, t, J=8Hz), 8.60 (1H, d, J=8Hz)

Example 70

(1) A mixture of 2,2-dimethyl-5-hydroxy-4-oxo-1,3-benzodioxane (2.00 g), 2-iodopropane (2.80 g) and potassium carbonate (2.85 g) in acetone (20 ml) was refluxed for 24 hours. The mixture was diluted with dichloromethane and filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (ethyl acetate/n-hexane = 1/8-1/4) to give 2,2-dimethyl-4-oxo-5-isopropoxy-1,3-benzodioxane (1.88 g) as oil.

NMR ($CDCl_3$, δ) : 1.44 (6H, d, J=7Hz), 1.70 (6H, s), 4.64 (1H, quint., J=7Hz), 6.51 (1H, d, J=8Hz), 6.62 (1H, d, J=8Hz), 7.40 (1H, t, J=8Hz)

(2) To a solution of 2,2-dimethyl-4-oxo-5-isopropoxy-1,3-benzodioxane (1.00 g) in methanol (5 ml) was added sodium methoxide (252 mg) in one portion at ambient temperature. After stirring for 1 hour, the mixture was acidified with 1N hydrochloric acid and extracted with dichloromethane. The organic phase was concentrated in vacuo to give methyl 2-hydroxy-6-isopropoxybenzoate (816 mg) as oil.

NMR ($CDCl_3$, δ) : 1.35 (6H, d, J=7Hz), 3.92 (3H, s), 4.56 (1H, quint., J=7Hz), 6.41 (1H, d, J=8Hz), 6.56 (1H, d, J=8Hz), 7.29 (1H, t, J=8Hz)

(3) A mixture of methyl 2-hydroxy-6-isopropoxybenzoate (810 mg) and sodium hydride (97 mg, 60% in oil) in 1,3-dimethyl-2-

imidazolidinone (6.5 ml) was stirred for 30 minutes with ice cooling. Additionally, the mixture was stirred for 1 hour at ambient temperature, and to the mixture was added 2,2,2-trifluoroethyl p-toluenesulfonate (1.03 g) and the mixture was stirred for 18 hours at 120°C. The resulting mixture was partitioned between ethyl acetate and 3% aqueous sodium bicarbonate. The organic phase was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/n-hexane = 1/8-1/6) to give methyl 2-isopropoxy-6-(2,2,2-trifluoroethoxy)benzoate (1.16 g) as oil.

NMR ($CDCl_3$, δ) : 1.31 (6H, d, J=7Hz), 3.90 (3H, s), 4.36 (2H, q, J=8Hz), 4.55 (1H, quint., J=7Hz), 6.50 (1H, d, J=8Hz), 6.68 (1H, d, J=8Hz), 7.28 (1H, m)

(4) A mixture of 2-isopropoxy-6-(2,2,2-trifluoroethoxy)-benzoate (1.13 g) and 1N aqueous sodium hydroxide (5 ml) in ethanol (5 ml) was refluxed for 8 hours. After concentration in vacuo, the mixture was partitioned between dichloromethane and 1N hydrochloric acid. The organic phase was concentrated in vacuo and the residue was crystallized from n-hexane to give 2-isopropoxy-6-(2,2,2-trifluoroethoxy)benzoic acid (728 mg).

mp : 117-118°C

NMR ($CDCl_3$, δ) : 1.38 (6H, d, J=7Hz), 4.40 (2H, q, J=8Hz), 4.63 (1H, quint., J=7Hz), 6.59 (1H, d, J=8Hz), 6.73 (1H, d, J=8Hz), 7.33 (1H, t, J=8Hz)

(5) 1-(Morpholinocarbonyl)methyl-4-[2-isopropoxy-6-(2,2,2-trifluoroethoxy)benzoylamino]-2-trifluoromethyl-1H-benzimidazole was obtained from 2-isopropoxy-6-(2,2,2-trifluoroethoxy)benzoic acid and 4-amino-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole according to a similar manner to that of Example 66-(3).

mp : 243-244°C

NMR ($CDCl_3$, δ) : 1.35 (6H, d, J=7Hz), 3.57-3.70 (4H, m), 3.70-3.84 (4H, m), 4.43 (2H, q, J=8Hz), 4.63 (1H, quint., J=7Hz), 5.08 (2H, s), 6.62 (1H, d, J=8Hz), 6.74 (1H, d, J=8Hz), 7.01 (1H, d, J=8Hz), 7.35 (1H, t, J=8Hz), 7.56 (1H, t, J=8Hz), 8.51 (1H, d, J=8Hz), 8.82 (1H, br s)

Example 71

(1) Methyl 2-chloro-6-(2,2,2-trifluoroethoxy)benzoate was obtained from methyl 2-chloro-6-hydroxybenzoate and 2,2,2-trifluoroethyl p-toluenesulfonate according to a similar manner to that of Example 70-(3).
NMR ($CDCl_3$, δ) : 3.95 (3H, s), 4.39 (2H, q, J=8Hz), 6.84 (1H, d, J=8Hz), 7.12 (1H, d, J=8Hz), 7.31 (1H, t, J=8Hz)

(2) 2-Chloro-6-(2,2,2-trifluoroethoxy)benzoic acid was obtained according to a similar manner to that of Example 70-(4).
mp : 98-100°C
NMR (DMSO-d_6, δ) : 4.87 (2H, q, J=8Hz), 7.19 (1H, d, J=8Hz), 7.22 (1H, d, J=8Hz), 7.43 (1H, t, J=8Hz)

(3) 4-[2-Chloro-6-(2,2,2-trifluoroethoxy)benzoylamino]-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole was obtained from 2-chloro-6-(2,2,2-trifluoroethoxy)benzoic acid and 4-amino-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole according to a similar manner to that of Example 66-(3).
mp : 242-243°C
NMR ($CDCl_3$, δ) : 3.58-3.70 (4H, m), 3.70-3.83 (4H, m), 5.09 (2H, s), 6.91 (1H, d, J=8Hz), 7.06 (1H, d, J=8Hz), 7.19 (1H, d, J=8Hz), 7.38 (1H, t, J=8Hz), 7.47 (1H, t, J=8Hz), 8.54 (1H, d, J=8Hz), 8.51 (1H, s)

Example 72

(1) Methyl 2-chloro-6-(2-methoxyethoxy)benzoate was obtained from methyl 2-chloro-6-hydroxybenzoate and 2-chloroethyl methyl ether according to a similar manner to that of Example 70-(3).
NMR ($CDCl_3$, δ) : 3.41 (3H, s), 3.71 (2H, t, J=6Hz), 3.93 (3H, s), 4.15 (2H, t, J=6Hz), 6.87 (1H, d, J=8Hz), 7.00 (1H, d, J=8Hz), 7.26 (1H, t, J=8Hz)

(2) 2-Chloro-6-(2-methoxyethoxy)benzoic acid was obtained according to a similar manner to that of Example 70-(4).
NMR ($CDCl_3$, δ) : 3.43 (3H, s), 3.75 (2H, t, J=6Hz), 4.23 (2H, t, J=6Hz), 6.89 (1H, d, J=8Hz), 7.07 (1H, d, J=8Hz), 7.30 (1H, t, J=8Hz)

(3) 4-[2-Chloro-6-(2-methoxyethoxy)benzoylamino]-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole was obtained from 2-chloro-6-(2-methoxyethoxy)benzoic acid and 4-amino-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole according to a similar manner to that of Example 66-(3).
mp : 229-230°C
NMR ($CDCl_3$, δ) : 2.25 (3H, s), 3.57-3.83 (12H, m), 4.20 (2H, t, J=6Hz), 5.08 (2H, s), 6.92 (1H, d, J=8Hz), 7.03 (1H, d, J=8Hz), 7.07 (1H, d, J=8Hz), 7.30 (1H, t, J=8Hz), 7.43 (1H, t, J=8Hz), 8.55 (1H, d, J=8Hz), 8.71 (1H, br s)

Example 73

The following compounds were obtained according to a similar manner to that of Example 66-(3).

(1) 4-(2,6-Dimethoxybenzoylamino)-1-(morpholinocarbonyl)-methyl-2-trifluoromethyl-1H-benzimidazole
(from 1,2-dimethoxybenzoic acid and 4-amino-1-

(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole)

mp : 225-229°C

NMR ($CDCl_3$, δ) : 3.55-3.69 (4H, m), 3.69-3.81 (4H, m), 3.84 (2H, s), 6.62 (2H, d, J=8Hz), 6.98 (1H, d, J=8Hz), 7.35 (1H, t, J=8Hz), 7.40 (1H, t, J=8Hz), 8.58 (1H, d, J=8Hz), 8.73 (1H, br s)

(2) 4-(2,6-Dichloro-3-methoxybenzoylamino)-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole

(from 2,6-dichloro-3-methoxybenzoic acid and 4-amino-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole)

mp : 236-238°C

NMR ($CDCl_3$, δ) : 3.54-3.70 (4H, m), 3.70-3.83 (4H, m), 3.95 (3H, s), 5.08 (2H, s), 6.97 (1H, d, J=8Hz), 7.07 (1H, d, J=8Hz), 7.33 (1H, d, J=8Hz), 7.47 (1H, t, J=8Hz), 8.53-8.61 (2H, m)

(3) 4-(2-Chloro-6-methoxybenzoylamino)-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole

(from 2-chloro-6-methoxybenzoic acid and 4-amino-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole)

mp : 218-219°C

NMR ($CDCl_3$, δ) : 3.56-3.69 (4H, m), 3.69-3.72 (4H, m), 3.86 (3H, s), 5.06 (2H, s), 6.89 (1H, d, J=8Hz), 7.04 (1H, t, J=8Hz), 7.33 (1H, t, J=8Hz), 7.45 (1H, t, J=8Hz), 8.58 (1H, d, J=8Hz), 8.64 (1H, br s)

Example 74

A mixture of 1-carboxymethyl-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (200

mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (98 mg) and 1-hydroxybenzotriazole (69 mg) in N,N-dimethylformamide (2 ml) was stirred for 30 minutes at room temperature. To the solution was added 2-(N-hydroxyamidino)pyridine (70 mg), and the mixture was stirred for 2 hours at room temperature. To the mixture was added water and the separated solid was collected. A mixture of the solid in a mixture of acetic acid (1 ml) and N,N-dimethylformamide (1.5 ml) was stirred for 2 hours at 100°C. The mixture was poured into water and extracted with ethyl acetate. The extract was washed successively with saturated aqueous sodium bicarbonate solution and brine, and concentrated in vacuo. The residue was crystallized from ethanol to give 4-(2,6-dichlorobenzoylamino)-1-[3-(2-pyridyl)-1,2,4-oxadiazol-5-yl]methyl-2-trifluoromethyl-1H-benzimidazole. The product was dissolved in 10% methanolic hydrogen chloride, and the solution was concentrated in vacuo to give 4-(2,6-dichlorobenzoylamino)-1-[3-(2-pyridyl)-1,2,4-oxadiazol-5-yl]methyl-2-trifluoromethyl-1H-benzimidazole hydrochloride (129 mg).

mp : 248-250°C

NMR (DMSO-d_6, δ) : 6.30 (2H, s), 7.43-7.63 (5H, m), 7.70 (1H, d, J=8Hz), 7.92-8.00 (2H, m), 8.29 (1H, d, J=8Hz), 8.72 (1H, d, J=6Hz)

Example 75

4-(2,6-Dichlorobenzoylamino)-1-{2-[(pyridin-3-yl)carbonylamino]ethyl}-2-trifluoromethyl-1H-benzimidazole hydrochloride was obtained from 1-(2-aminoethyl)-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole and nicotinoyl chloride hydrochloride according to a similar manner to that of Example 1-(2).

mp : 204-213°C

NMR (DMSO-d_6, δ) : 3.76 (2H, q, J=5Hz), 4.62 (2H, t, J=5Hz), 7.40-7.70 (6H, m), 4.18-8.25 (2H, m), 8.78

(1H, d, J=5Hz), 8.93 (1H, s), 9.07 (1H, t, J=5Hz)

Example 76

To a mixture of 4-(2,6-dichlorobenzoylamino)-1H-benzimidazole (100 mg), 2-(3-pyridyloxy)ethanol (48 mg), triphenylphosphine (112 mg) in dichloromethane (2 ml) was added diethyl azodicarboxylate (51 mg) with ice cooling. The reaction mixture was stirred for 18 hours at ambient temperature. The separated solid was collected and the solid was purified by preparative TLC (eluted with 1% methanol in dichloromethane). The obtained solid was triturated with diethyl ether and collected to give 4-(2,6-dichlorobenzoylamino)-1-[2-(3-pyridyloxy)ethyl]-2-trifluoromethyl-1H-benzimidazole (25 mg).

mp : 166-167°C

NMR (DMSO-d_6, δ) : 4.46 (2H, t, J=5Hz), 4.86 (2H, t, J=5Hz), 7.26-7.32 (2H, m), 7.44-7.58 (3H, m), 7.70 (1H, d, J=8Hz), 8.14-8.20 (2H, m), 8.24 (1H, d, J=8Hz), 11.16 (1H, s)

its hydrochloride

mp : 215-218°C

NMR (DMSO-d_6, δ) : 4.58 (2H, t, J=6Hz), 4.90 (2H, t, J=6Hz), 7.44-7.57 (4H, m), 7.66 (1H, m), 7.70 (1H, d, J=8Hz), 7.76 (1H, dd, J=2Hz, 8Hz), 8.23 (1H, d, J=8Hz), 8.37 (1H, d, J=6Hz), 8.43 (1H, d, J=2Hz)

Example 77

A mixture of 4-(2,6-dichlorobenzoylamino)-1-(2-methylsulfonyloxyethyl)-2-trifluoromethyl-1H-benzimidazole (50 mg) and potassium iodide (19 mg) in N,N-dimethylformamide (0.5 ml) was stirred for 2 hours at 60°C. After cooling to ambient temperature, to the mixture was added 1-methyl-2-mercaptoimidazole (13 mg). The resulting mixture was stirred for 2 hours at ambient temperature and to the mixture was

added water. The separated solid was purified by preparative TLC (5% methanol in dichloromethane). The separated oil was crystallized from a mixture of ethanol and water to give 4-(2,6-dichlorobenzoylamino)-1-[2-(1-methylimidazol-2-ylthio)ethyl]-2-trifluoromethyl-1H-benzimidazole (30 mg).

mp : 177-178°C

NMR ($CDCl_3$, δ) : 3.48 (2H, t, J=7Hz), 3.53 (3H, s), 4.75 (2H, t, J=7Hz), 6.99 (1H, s), 7.18 (1H, s), 7.30-7.42 (4H, m), 7.48 (1H, t, J=8Hz), 8.56 (1H, d, J=8Hz), 8.60 (1H, br s)

its hydrochloride

mp : 223-226°C

NMR (DMSO-d_6, δ) : 3.60-3.70 (5H, m), 4.69 (2H, t, J=7Hz), 7.46-7.62 (5H, m), 7.65 (1H, s), 7.70 (1H, s), 8.22 (1H, d, J=8Hz)

Example 78

4-(2,6-Dichlorobenzoylamino)-1-[2-(thiazolin-2-ylthio)ethyl]-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 77.

mp : 175-183°C

NMR ($CDCl_3$, δ) : 3.38-3.52 (4H, m), 4.21-4.35 (2H, m), 4.60-4.77 (2H, m), 7.20-7.30 (1H, m), 7.30-7.43 (2H, m), 7.43-7.61 (2H, m), 8.58 (1H, m)

Example 79

(1) To a mixture of 4-(2,6-dichlorobenzoylamino)-1-(N-hydroxyamidino)methyl-2-trifluoromethyl-1H-benzimidazole (150 mg) and triethylamine (51 mg) in dichloromethane (2 ml) was added ethyl chloroformate (44 mg) with ice cooling. The mixture was stirred for 1 hour at ambient temperature. The resulting mixture was washed successively with water and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica

gel (eluted with 1% methanol in dichloromethane) to give 4-(2,6-dichlorobenzoylamino)-1-[(N-ethoxycarbonyloxy)-amidinomethyl]-2-trifluoromethyl-1H-benzimidazole (128 mg) as amorphous.

NMR ($CDCl_3$, δ) : 1.38 (3H, t, J=7Hz), 4.33 (2H, q, J=7Hz), 4.70-4.90 (2H, m), 5.10 (2H, s), 7.31-7.45 (3H, m), 7.45-7.59 (2H, m), 8.54-8.67 (2H, m)

(2) A mixture of 4-(2,6-dichlorobenzoylamino)-1-[(N-ethoxycarbonyloxy)amidinomethyl]-2-trifluoromethyl-1H-benzimidazole (125 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.3 ml) in toluene (1.5 ml) was stirred for 30 minutes at ambient temperature. After dilution with ethyl acetate, the resulting mixture was washed successively with 1N hydrochloric acid and brine, dried over sodium sulfate, and evaporated in vacuo. The obtained oil was crystallized from a mixture of ether and n-hexane (1:1) to give 4-(2,6-dichlorobenzoylamino)-1-(4,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)methyl-2-trifluoromethyl-1H-benzimidazole (77 mg).

mp : 242-244°C

NMR ($CDCl_3$, δ) : 5.43 (2H, s), 7.24-7.32 (1H, m), 7.36-7.45 (3H, m), 7.56 (1H, t, J=8Hz), 8.61 (1H, d, J=8Hz)

Example 80

To a mixture of 4-[N-(2,6-dichlorophenyl)carbamoyl]-1-(2-hydroxyethyl)-2-trifluoromethyl-1H-benzimidazole (100 mg), hydantoin (31 mg) and triphenylphosphine (113 mg) in N,N-dimethylformamide (1 ml) was added diethyl azodicarboxylate (75 mg) at ambient temperature. The mixture was stirred for 30 minutes at 80°C. The resulting mixture was partitioned between ethyl acetate and 3% aqueous sodium bicarbonate. The organic phase was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/n-hexane =

1/1 then ethyl acetate only) and the obtained oil was purified by preparative thin layer chromatography (TLC) (ethyl acetate/n-hexane = 2/1). The obtained oil was crystallized from a mixture of ethanol and water to give 4-[N-(2,6-dichlorophenyl)carbamoyl]-1-[2-(2,4-dioxoimidazolidin-3-yl)ethyl]-2-trifluoromethyl-1H-benzimidazole (25 mg).

mp : 212-214°C

NMR ($CDCl_3$, δ) : 3.83 (2H, s), 4.05 (2H, t, J=7Hz), 4.65 (2H, t, J=7Hz), 5.38 (1H, br s), 7.21 (1H, t, J=8Hz), 7.43 (2H, d, J=8Hz), 7.62 (1H, t, J=8Hz), 7.78 (1H, d, J=8Hz), 8.38 (1H, d, J=8Hz)

Example 81

(1) 4-Ethoxycarbonyl-1-methoxymethyl-2-trifluoromethyl-1H-benzimidazole was obtained by reacting 4-ethoxycarbonyl-2-trifluoromethyl-1H-benzimidazole with chloromethyl methyl ether according to a similar manner to that of Example 5.

mp : 54-56°C

NMR ($CDCl_3$, δ) : 1.48 (3H, t, J=6Hz), 3.32 (3H, s), 4.52 (2H, q, J=6Hz), 5.69 (2H, s), 7.52 (1H, t, J=8Hz), 7.85 (1H, d, J=8Hz), 8.08 (1H, d, J=8Hz)

(2) 4-Carboxy-1-methoxymethyl-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 51-(4).

mp : 127-129°C

NMR ($CDCl_3$, δ) : 3.39 (3H, s), 5.75 (2H, s), 7.66 (1H, t, J=8Hz), 7.92 (1H, d, J=8Hz), 8.28 (1H, d, J=8Hz)

(3) 4-[N-(2,6-Dichlorophenyl)carbamoyl]-1-methoxymethyl-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 45.

mp : 122-123°C

NMR ($CDCl_3$, δ) : 3.40 (3H, s), 5.74 (2H, s), 7.22 (1H,

t, J=8Hz), 7.45 (2H, d, J=8Hz), 7.64 (1H, t, J=8Hz), 7.87 (1H, d, J=8Hz), 8.42 (1H, d, J=8Hz)

(4) A mixture of 4-[N-(2,6-dichlorophenyl)carbamoyl]-1-methoxymethyl-2-trifluoromethyl-1H-benzimidazole (35 mg) and concentrated hydrochloric acid (0.042 ml) in tetrahydrofuran (0.46 ml) was stirred for 1 hour at ambient temperature. To the mixture was added 8N hydrogen chloride in ethanol (0.2 ml) and refluxed for 5 hours, and the mixture was poured into sodium bicarbonate - ethyl acetate solution. The organic layer was dried and concentrated in vacuo. The residue was crystallized from isopropyl ether to give 4-[N-(2,6-dichlorophenyl)carbamoyl]-2-trifluoromethyl-1H-benzimidazole (24 mg).

mp : >250°C

NMR ($CDCl_3$, δ) : 7.22 (1H, t, J=8Hz), 7.45 (2H, d, J=8Hz), 7.53 (1H, t, J=8Hz), 7.72 (1H, d, J=8Hz), 8.32 (1H, d, J=8Hz)

(5) 4-[N-(2,6-Dichlorophenyl)carbamoyl]-1-[2-(4-methylthiazol-5-yl)ethyl]-2-trifluoromethyl-1H-benzimidazole was obtained from 4-[N-(2,6-dichlorophenyl)carbamoyl]-2-trifluoromethyl-1H-benzimidazole and 4-methyl-5-thiazoleethanol according to a similar manner to that of Example 80.

mp : 205-206°C

NMR ($CDCl_3$, δ) : 2.30 (3H, s), 3.38 (2H, t, J=7Hz), 7.44 (2H, d, J=8Hz), 7.49 (1H, d, J=8Hz), 7.59 (1H, t, J=8Hz), 8.39 (1H, d, J=8Hz), 8.62 (1H, s)

Example 82

(1) 4-Ethoxycarbonyl-1-(2-phenoxyethyl)-2-trifluoromethyl-1H-benzimidazole was obtained from 4-ethoxycarbonyl-2-trifluoromethyl-1H-benzimidazole and 2-bromoethyl phenyl ether according to a similar manner to that of Example 5.

NMR ($CDCl_3$, δ) : 1.46 (3H, t, J=8Hz), 4.33 (2H, t, J=7Hz), 4.50 (2H, q, J=8Hz), 4.78 (2H, t, J=7Hz), 6.77 (2H, d, J=8Hz), 6.96 (1H, t, J=8Hz), 7.24 (2H, t, J=8Hz), 7.52 (1H, t, J=8Hz), 7.90 (1H, d, J=8Hz), 8.07 (1H, d, J=8Hz)

(2) 4-Carboxy-1-(2-phenoxyethyl)-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 51-(4).

mp : 133-134°C

NMR ($DMSO-d_6$, δ) : 4.36 (2H, t, J=7Hz), 4.90 (2H, t, J=8Hz), 6.80 (2H, d, J=8Hz), 6.90 (1H, t, J=8Hz), 7.22 (2H, t, J=8Hz), 7.60 (1H, t, J=8Hz), 7.92 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz)

(3) 4-[N-(2,6-Dichlorophenyl)carbamoyl]-1-(2-phenoxyethyl)-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 45.

mp : 184-185°C

NMR ($CDCl_3$, δ) : 4.39 (2H, t, J=7Hz), 4.83 (2H, t, J=7Hz), 6.80 (2H, d, J=8Hz), 6.98 (1H, t, J=8Hz), 7.19-7.30 (3H, m), 7.43 (2H, d, J=8Hz), 7.66 (1H, t, J=8Hz), 7.92 (1H, d, J=8Hz), 8.40 (1H, d, J=8Hz)

Example 83

(1) 4-Ethoxycarbonyl-1-(4-methoxybenzyl)-2-trifluoromethyl-1H-benzimidazole was obtained from 4-ethoxycarbonyl-2-trifluoromethyl-1H-benzimidazole and 4-methoxybenzyl chloride according to a similar manner to that of Example 5.

NMR ($CDCl_3$, δ) : 1.48 (3H, t, J=7Hz), 3.78 (3H, s), 5.51 (2H, s), 6.84 (2H, d, J=8Hz), 7.04 (2H, d, J=8Hz), 7.40 (1H, t, J=8Hz), 7.50 (1H, d, J=8Hz), 8.03 (1H, d, J=8Hz)

(2) 4-Carboxy-1-(4-methoxybenzyl)-2-trifluoromethyl-1H-

benzimidazole was obtained according to a similar manner to that of Example 51-(4).

mp : 134-135°C

NMR (DMSO-d_6, δ) : 3.70 (3H, s), 5.67 (2H, s), 6.90 (2H, d, J=8Hz), 7.09 (2H, d, J=8Hz), 7.53 (1H, t, J=8Hz), 7.91 (1H, d, J=8Hz), 7.96 (1H, d, J=8Hz)

(3) 4-[N-(2,6-Dichlorophenyl)carbamoyl]-1-(4-methoxybenzyl)-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 45.

mp : 158-159°C

NMR ($CDCl_3$, δ) : 3.79 (3H, s), 5.56 (2H, s), 6.89 (2H, d, J=8Hz), 7.12 (2H, d, J=8Hz), 7.19-7.27 (1H, m), 7.43 (2H, d, J=8Hz), 7.49-7.53 (2H, m), 8.36 (1H, m)

Example 84

(1) 4-[N-(2-Methyl-6-methoxyphenyl)carbamoyl]-1-(4-methoxybenzyl)-2-trifluoromethyl-1H-benzimidazole was obtained from 4-carboxy-1-(4-methoxybenzyl)-2-trifluoromethyl-1H-benzimidazole and 2-methoxy-6-methylaniline according to a similar manner to that of Example 45.

mp : 172-173°C

NMR ($CDCl_3$, δ) : 2.36 (3H, s), 3.80 (3H, s), 3.87 (3H, s), 5.54 (2H, s), 6.83-6.95 (4H, m), 7.11 (2H, d, J=8Hz), 7.20 (1H, t, J=8Hz), 7.56-7.52 (2H, m), 8.34 (1H, m)

(2) A mixture of 4-[N-(2-methyl-6-methoxyphenyl)carbamoyl]-1-(4-methoxybenzyl)-2-trifluoromethyl-1H-benzimidazole (380 mg) in trifluoroacetic acid (3 ml) was stirred for 2 hours at 70°C. The resulting mixture was concentrated followed by azeotropic removal of the residual trifluoroacetic acid with toluene. The residue was purified by column chromatography on silica gel (ethyl acetate/n-hexane = 1/4-1/3). The

obtained oil was crystallized from ethyl acetate to give 4-[N-(2-methyl-6-methoxyphenyl)carbamoyl]-2-trifluoromethyl-1H-benzimidazole (78 mg).

mp : >250°C

NMR (DMSO-d_6, δ) : 2.21 (3H, s), 3.76 (3H, s), 6.91 (1H, d, J=8Hz), 6.97 (1H, d, J=8Hz), 7.61 (1H, m), 7.96 (1H, m), 8.11 (1H, d, J=8Hz)

(3) 4-[N-(2-Methyl-6-methoxyphenyl)carbamoyl]-1-(2-acetoxyethyl)-2-trifluoromethyl-1H-benzimidazole was obtained from 4-[N-(2-methyl-6-methoxyphenyl)carbamoyl]-2-trifluoromethyl-1H-benzimidazole and 2-bromoethyl acetate according to a similar manner to that of Example 5.

NMR ($CDCl_3$, δ) : 2.00 (3H, s), 2.37 (3H, s), 3.83 (3H, s), 4.49 (2H, t, J=6Hz), 4.67 (2H, t, J=6Hz), 6.83 (2H, d, J=8Hz), 6.92 (2H, d, J=8Hz), 7.20 (1H, t, J=8Hz), 7.61 (1H, t, J=8Hz), 7.71 (1H, d, J=8Hz), 8.39 (1H, d, J=8Hz)

(4) 4-[N-(2-Methyl-6-methoxyphenyl)carbamoyl]-1-(2-hydroxyethyl)-2-trifluoromethyl-1H-benzimidazole was obtained from 4-[N-(2-methyl-6-methoxyphenyl)carbamoyl]-1-(2-acetoxyethyl-2-trifluoromethyl-1H-benzimidazole according to a similar manner to that of Example 51-(4).

mp : 184-185°C

NMR ($CDCl_3$, δ) : 2.05 (1H, t, J=7Hz), 2.35 (3H, s), 3.83 (3H, s), 4.06 (2H, q, J=7Hz), 4.54 (2H, t, J=7Hz), 6.83 (1H, d, J=8Hz), 6.92 (1H, d, J=8Hz), 7.20 (1H, t, J=8Hz), 7.57 (1H, t, J=8Hz), 7.79 (1H, d, J=8Hz), 8.30 (1H, d, J=8Hz)

Example 85

(1) 4-Ethoxycarbonyl-1-(pyridin-2-yl)methyl-2-trifluoromethyl-1H-benzimidazole was obtained from 4-ethoxycarbonyl-2-trifluoromethyl-1H-benzimidazole and

2-picolyl chloride hydrochloride according to a similar manner to that of Example 5.

mp : 96-98°C

NMR ($CDCl_3$, δ) : 1.48 (3H, t, J=6Hz), 4.52 (2H, q, J=6Hz), 5.60 (2H, s), 7.20-7.32 (2H, m), 7.40-7.50 (2H, m), 8.07 (1H, d, J=8Hz), 8.56 (1H, s), 8.59 (1H, d, J=5Hz)

(2) 4-Carboxy-1-(pyridin-2-yl)methyl-2-trifluoromethyl-1H-benzimidazole was obtained according to a similar manner to that of Example 51-(4).

mp : 169-172°C

NMR (DMSO-d_6, δ) : 5.82 (2H, s), 7.31-7.47 (2H, m), 7.57 (1H, t, J=8Hz), 8.95 (1H, d, J=8Hz), 8.02 (1H, d, J=8Hz), 8.48 (1H, s), 8.50 (1H, d, J=5Hz)

(3) 4-[N-(2,6-Dichlorophenyl)carbamoyl]-1-(pyridin-2-yl)methyl-2-trifluoromethyl-1H-benzimidazole hydrochloride was obtained according to a similar manner to that of Example 45.

mp : 190-202°C

NMR (DMSO-d_6, δ) : 5.98 (2H, s), 7.35 (1H, dd, J=5Hz, 3Hz), 7.40-7.51 (2H, m), 7.87 (1H, t, J=8Hz), 8.10 (1H, d, J=8Hz), 8.13 (1H, d, J=8Hz), 8.43 (1H, d, J=5Hz)

Example 86

A mixture of 4-amino-2-trifluoromethyl-1H-benzimidazole (7.68 g), 2,6-dichlorobenzoyl chloride (8.80 g) and triethylamine (5.80 g) in 1,3-dimethyl-2-imidazolidinone (61 ml) was stirred for 12 hours at ambient temperature. The mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic phase was washed successively with 3% aqueous sodium bicarbonate and brine, dried over sodium sulfate and evaporated in vacuo. The

residue was purified by column chromatography on silica gel (4% ethyl acetate in dichloromethane). The obtained first fraction was crystallized from a mixture of ethyl acetate and n-hexane to give 4-(2,6-dichlorobenzoylamino)-1-(2,6-dichlorobenzoyl)-2-trifluoromethyl-1H-benzimidazole (3.20 g).

mp : 210-212°C

NMR ($CDCl_3$, δ) : 6.13 (1H, m), 7.32 (1H, t, J=8Hz), 7.37-7.43 (3H, m), 7.50-7.60 (3H, m), 8.58-8.64 (2H, m)

Example 87

(1) A mixture of 4-[N-(2,6-dichlorophenyl)carbamoyl]-1-(2-hydroxyethyl)-2-trifluoromethyl-1H-benzimidazole (400 mg), acetic anhydride (117 mg) and 4-dimethylaminopyridine (117 mg) in dichloromethane (4 ml) was stirred for 1 hour at ambient temperature. The resulting solution was washed with saturated aqueous sodium bicarbonate and concentrated in vacuo to give 4-[N-(2,6-dichlorophenyl)carbamoyl]-1-(2-acetoxyethyl)-2-trifluoromethyl-1H-benzimidazole (375 mg) as oil.

NMR ($CDCl_3$, δ) : 2.00 (3H, s), 2.37 (3H, s), 3.83 (3H, s), 4.49 (2H, t, J=7Hz), 4.67 (2H, t, J=7Hz), 6.83 (1H, d, J=8Hz), 6.92 (1H, d, J=8Hz), 7.20 (1H, t, J=8Hz), 7.61 (1H, t, J=8Hz), 7.71 (1H, d, J=8Hz), 8.39 (1H, d, J=8Hz)

(2) To a solution of 4-[N-(2,6-dichlorophenyl)carbamoyl]-1-(2-acetoxyethyl)-2-trifluoromethyl-1H-benzimidazole (365 mg) in N,N-dimethylformamide (3.5 ml) was added 60% sodium hydride in oil (20 mg) with ice cooling. After stirring for 15 minutes, the mixture was stirred for 30 minutes at ambient temperature. The mixture was recooled on an ice bath, and to the mixture was added iodomethane (135 mg). After stirring for 12 hours at ambient temperature, to the mixture was added excess of 1N aqueous sodium hydroxide and the mixture was

stirred for 4 hours at ambient temperature. The resulting solution was partitioned between ethyl acetate and 3% aqueous sodium bicarbonate. The organic phase was concentrated in vacuo and the residue was purified by column chromatography on silica gel (1% methanol in dichloromethane). The obtained oil was crystallized from a mixture of ethanol and water to give 4-[N-(2,6-dichlorophenyl)-N-methylcarbamoyl]-1-(2-hydroxyethyl)-2-trifluoromethyl-1H-benzimidazole (167 mg).

mp : 156-158°C

NMR ($CDCl_3$, δ) : 1.79 (0.8H, t, J=7Hz), 1.95 (0.2H, t, J=7Hz), 3.18 (0.6H, s), 3.47 (2.4H, s), 3.86-3.99 (1.6H, m), 4.00-4.09 (0.4H, m), 4.40 (1.6H, t, J=7Hz), 4.51 (0.4H, t, J=7Hz), 7.00 (1H, t, J=8Hz), 7.10-7.20 (2H, m), 7.10-7.33 (1H, m), 7.48 (1.6H, t, J=8Hz), 7.53-7.70 (0.4H, m)

Example 88

A mixture of 1-(2-bromoethyl)-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (170 mg), dimethylamine hydrochloride (288 mg) and potassium carbonate (586 mg) in N,N-dimethylformamide (2 ml) was stirred for 1 hour at 85°C. To the mixture was added water and the separated solid was collected and dried. The crude product was purified by column chromatography on silica gel and the obtained oil was crystallized from hexane to give 4-(2,6-dichlorobenzoylamino)-1-vinyl-2-trifluoromethyl-1H-benzimidazole (85 mg).

mp : 160-162°C

NMR ($CDCl_3$, δ) : 5.54 (1H, d, J=8Hz), 5.76 (1H, d, J=15Hz), 7.14 (1H, dd, J=8Hz, 15Hz), 7.27-7.45 (4H, m), 7.52 (1H, t, J=8Hz), 8.55-8.63 (2H, m)

Example 89

1-(2-Aminoethyl)-4-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-1H-benzimidazole hydrochloride was obtained

by treating the object compound of Example 28 according to a similar manner to that of Example 66-(7).

mp : 197-207°C

NMR (DMSO-d_6, δ) : 3.20-3.30 (2H, m), 4.66-4.73 (2H, m), 7.45-7.58 (4H, m), 7.22 (1H, d, J=8Hz), 8.18-8.30 (4H, m)

Example 90

A mixture of 4-[N-(2,6-dichlorophenyl)carbamoyl]-2-trifluoromethyl-1H-benzimidazole (374 mg), ethyl bromoacetate (184 mg) and potassium carbonate (414 mg) in N,N-dimethylformamide (3 ml) was stirred for 3 days at ambient temperature. The resulting mixture was partitioned between ethyl acetate and 3% aqueous sodium bicarbonate and the separated organic phase was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/n-hexane = 1/3).

(1) The first fraction was crystallized from a mixture of ethanol and water to give 4-[N-(2,6-dichlorophenyl)-carbamoyl]-1-ethoxycarbonylmethyl-2-trifluoromethyl-1H-benzimidazole (184 mg).

mp : 193-194°C

NMR ($CDCl_3$, δ) : 1.30 (3H, t, J=7Hz), 4.30 (2H, q, J=7Hz), 5.11 (2H, s), 7.22 (1H, t, J=8Hz), 7.44 (2H, d, J=8Hz), 7.58-7.69 (2H, m), 8.41 (1H, d, J=8Hz)

(2) The second fraction was crystallized from a mixture of ethanol and water to give 4-[N-(2,6-dichlorophenyl)-N-(ethoxycarbonylmethyl)carbamoyl]-1-ethoxycarbonylmethyl-2-trifluoromethyl-1H-benzimidazole (167 mg).

mp : 193-194°C

NMR ($CDCl_3$, δ) : 1.20 (3H, t, J=7Hz), 1.32 (3H, t,

J=7Hz), 4.15-4.31 (4H, m), 4.60 (2H, s), 4.93 (2H, s), 7.00 (1H, t, J=8Hz), 7.17 (2H, d, J=8Hz), 7.22-7.30 (3H, m), 7.50 (1H, m)

Example 91

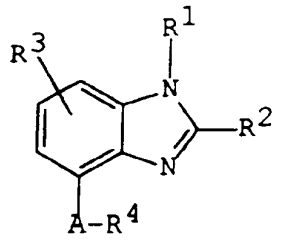
A mixture of 4-amino-1-(morpholinocarbonyl)methyl-2-trifluoromethyl-1H-benzimidazole (200 mg) and 2-nitrobenzoyl chloride (136 mg) in dichloromethane (1.5 ml) was stirred at ambient temperature overnight. The mixture was diluted with CH_2Cl_2 (1 ml) and washed with water. The organic phase was dried, filtered and concentrated in vacuo. The residual solid was washed with hot ethanol (5 ml) and allowed to cool to ambient temperature. The precipitate was filtered and air-dried to give 1-(morpholinocarbonyl)methyl-4-(2-nitrobenzoylamino)-2-trifluoromethyl-1H-benzimidazole (280 mg).

mp : 237-245°C

NMR ($CDCl_3$, δ) : 3.50-3.67 (4H, m), 3.70-3.84 (4H, m), 5.07 (2H, s), 7.01 (1H, d, J=8Hz), 7.38 (1H, t, J=8Hz), 7.61-7.81 (3H, m), 8.18 (1H, d, J=8Hz), 8.40 (1H, d, J=9Hz), 8.78 (1H, br s)

C L A I M S

1. A compound of the formula :



wherein

R^1 is acyl, lower alkenyl or lower alkyl optionally substituted with substituent(s) selected from the group consisting of aryl, substituted aryl, a heterocyclic group, a substituted heterocyclic group, hydroxy, substituted hydroxy, cyano, halogen, amino, substituted amino, acyl, mercapto, substituted mercapto, hydroxyamidino, substituted hydroxyamidino and substituted hydrazono, and

R^2 is hydrogen, lower alkyl, hydroxy(lower)alkyl, halo(lower)alkyl, lower alkoxy, lower alkylthio, acyl or cyano, or

R^1 and R^2 are taken together to form lower alkylene or lower alkenylene, each of which may include O, S or N-R^5 in the chain, in which R^5 is hydrogen or lower alkyl,

R^3 is hydrogen or halogen,

R^4 is a heterocyclic group or aryl, each of which may be substituted with suitable substituent(s), and

A is $-CON(R^9)-$ or $-N(R^{10})CO-$,

in which R^9 is hydrogen, lower alkyl or substituted lower alkyl, and

R^{10} is hydrogen, lower alkyl or substituted lower alkyl,

and pharmaceutically acceptable salts thereof.

2. A compound of claim 1, wherein

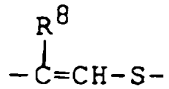
R^1 is lower alkanoyl; haloaroyl; lower alkenyl; lower alkyl; or lower alkyl substituted with substituent(s) selected from the group consisting of aryl, aryl substituted with nitro, aryl substituted with cyano, aryl substituted with lower alkoxy, a heterocyclic group, a heterocyclic group substituted with a heterocyclic group, a heterocyclic group substituted with lower alkyl, a heterocyclic group substituted with halogen, a heterocyclic group substituted with one or two oxo(s), hydroxy, hydroxy substituted with lower alkyl, hydroxy substituted with lower alkanoyl, hydroxy substituted with carboxy(lower)alkanoyl, hydroxy substituted with succinimidooxycarbonyl(lower)alkanoyl, hydroxy substituted with diphosphono(lower)alkylcarbamoyl-(lower)alkanoyl, hydroxy substituted with aryl, hydroxy substituted with ar(lower)alkyl, hydroxy substituted with a heterocyclic group, cyano, halogen, amino, lower alkanoylamino, lower alkylsulfonylamino, heterocycliccarbonylamino, lower alkanoyl, aroyl, carboxy, lower alkoxycarbonyl, heterocycliccarbonyl, heterocycliccarbonyl substituted with lower alkyl, heterocycliccarbonyl substituted with lower alkanoyl, heterocycliccarbonyl substituted with halogen, heterocycliccarbonyl substituted with aryl, carbamoyl, lower alkylcarbamoyl, carboxy(lower)alkylcarbamoyl, lower alkoxycarbonyl(lower)alkylcarbamoyl, cyclo(lower)alkylcarbamoyl, halo(lower)alkylcarbamoyl, cyano(lower)alkylcarbamoyl, hydroxy(lower)-

alkylcarbamoyl, lower alkoxy(lower)alkylcarbamoyl, lower alkanoyloxy(lower)alkylcarbamoyl, lower alkoxycarbamoyl, aminocarbamoyl, tert-butoxycarbonylaminocarbamoyl, carbamoyl(lower)alkylcarbamoyl, hydroxy(lower)alkylcarbamoyl(lower)alkylcarbamoyl, arylsulfonylcarbamoyl, arylcarbamoyl, lower alkoxy-arylcarbamoyl, halo(lower)alkyl-arylcarbamoyl, lower alkylamino-arylcarbamoyl, ar(lower)alkylcarbamoyl, halo(lower)alkyl-ar(lower)alkylcarbamoyl, heterocyclic-(lower)alkylcarbamoyl, lower alkyl-heterocyclic(lower)-alkylcarbamoyl, heterocycliccarbamoyl, lower alkyl-heterocycliccarbamoyl, halo(lower)alkyl-heterocycliccarbamoyl, lower alkoxy-heterocycliccarbamoyl, lower alkylthio-heterocycliccarbamoyl, sulfamoyl-heterocycliccarbamoyl, N-heterocyclic-N-(lower alkyl)carbamoyl, phthaloyl, mercapto, mercapto substituted with a heterocyclic group, mercapto substituted with a heterocyclic group substituted with lower alkyl, hydroxyamidino, hydroxyamidino substituted with lower alkoxycarbonyl, and hydrazono substituted with a heterocyclic group; and

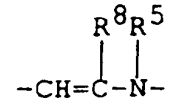
R^2 is hydrogen, lower alkyl, hydroxy(lower)alkyl, halo(lower)alkyl, lower alkoxy, lower alkylthio, lower alkylsulfonyl, carbamoyl or cyano, or

R^1 and R^2 are taken together to form a group of the formula :

$$-CH_2-CH_2-CH_2-S-,$$



$$-CH=CH-S-,$$



$$-CH=C-N- ,$$

in which R^5 and R^8 are each hydrogen or lower alkyl,

R^3 is hydrogen or halogen,

R^4 is aryl substituted with substituent(s) selected from the group consisting of halogen, lower alkyl, lower alkoxy, lower alkoxy(lower)alkoxy, halo(lower)alkoxy, lower alkanoyl, lower alkoxycarbonyl(lower)alkenyl, hydroxy(lower)alkyl and lower alkyldiarylsilyloxy-(lower)alkyl, and

A is $-\overset{\overset{R^9}{|}}{CON}-$ or $-\overset{\overset{R^{10}}{|}}{NCO}-$,

in which R^9 is hydrogen, lower alkyl or lower alkoxycarbonyl(lower)alkyl, and

R^{10} is hydrogen, lower alkyl or lower alkoxycarbonyl(lower)alkyl.

3. A compound of claim 2, wherein

R^1 is lower alkanoyl; dichlorobenzoyl; lower alkenyl; lower alkyl; or lower alkyl substituted with substituent(s) selected from the group consisting of phenyl, phenyl substituted with nitro, phenyl substituted with cyano, phenyl substituted with lower alkoxy, morpholinyl, piperazinyl, pyridyl, furyl, thiazolyl, oxadiazolyl, dihydrooxadiazolyl, tetrazolyl, imidazolyl, imidazolidinyl, pyrrolidinyl, oxiranyl, benzodioxolyl, phthalimido, oxadiazolyl substituted with pyridyl, piperazinyl substituted with lower alkyl, oxadiazolyl substituted with lower alkyl, imidazolyl, substituted with lower alkyl, thiazolyl substituted with lower alkyl, benzodioxolyl substituted with halogen, 4,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl, imidazolidinyl substituted with two oxos, hydroxy, hydroxy substituted with lower alkyl, hydroxy substituted with lower alkanoyl, hydroxy substituted with carboxy(lower)alkanoyl, hydroxy substituted with

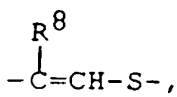
succinimidooxycarbonyl(lower)alkanoyl, hydroxy substituted with diphosphono(lower)alkylcarbamoyl-(lower)alkanoyl, hydroxy substituted with phenyl, hydroxy substituted with phenyl(lower)alkyl, hydroxy substituted with pyridyl, cyano, halogen, amino, lower alkanoylamino, lower alkylsulfonylamino, morpholinylcarbonylamino, pyridylcarbonylamino, lower alkanoyl, benzoyl, carboxy, lower alkoxycarbonyl, morpholinylcarbonyl, pyridylcarbonyl, pyrrolidinylcarbonyl, piperazinylcarbonyl, thienylcarbonyl, morpholinylcarbonyl substituted with lower alkyl, piperazinylcarbonyl substituted with lower alkanoyl, thienylcarbonyl substituted with halogen, piperazinylcarbonyl substituted with phenyl, carbamoyl, lower alkylcarbamoyl, carboxy(lower)alkylcarbamoyl, lower alkoxycarbonyl(lower)alkylcarbamoyl, cyclo(lower)alkylcarbamoyl, halo(lower)alkylcarbamoyl, cyano(lower)alkylcarbamoyl, hydroxy(lower)-alkylcarbamoyl, lower alkoxy(lower)alkylcarbamoyl, lower alkanoyloxy(lower)alkylcarbamoyl, lower alkoxycarbamoyl, aminocarbamoyl, tert-butoxycarbonylaminocarbamoyl, carbamoyl(lower)alkylcarbamoyl, hydroxy(lower)alkylcarbamoyl(lower)alkylcarbamoyl, phenylsulfonylcarbamoyl, phenylcarbamoyl, lower alkoxy-phenylcarbamoyl, halo(lower)alkyl-phenylcarbamoyl, lower alkylamino-phenylcarbamoyl, phenyl(lower)alkylcarbamoyl, halo(lower)alkyl-phenyl(lower)alkylcarbamoyl, pyridyl-(lower)alkylcarbamoyl, furyl(lower)alkylcarbamoyl, tetrahydrofuryl(lower)alkylcarbamoyl, oxadiazolyl(lower)alkylcarbamoyl, indolyl(lower)alkylcarbamoyl, benzodioxolyl(lower)alkylcarbamoyl, imidazolyl(lower)alkylcarbamoyl, lower alkyl-oxadiazolyl(lower)alkylcarbamoyl,

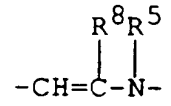
pyridylcarbamoyl, morpholinylcarbamoyl, thiazolylcarbamoyl, thiadiazolylcarbamoyl, oxazolylcarbamoyl, isoxazolylcarbamoyl, lower alkyl-oxazolylcarbamoyl, lower alkyl-isoxazolylcarbamoyl, lower alkyl-thiadiazolylcarbamoyl, halo(lower)alkyl-thiadiazolylcarbamoyl, lower alkoxy-pyridylcarbamoyl, lower alkylthio-thiadiazolylcarbamoyl, sulfamoyl-thiadiazolylcarbamoyl, N-pyridyl-N-(lower alkyl)carbamoyl, phthaloyl, mercapto, pyridylthio, imidazolylthio, thiazolinylthio, thiadiazolylthio, imidazopyridylthio, lower alkylimidazolylthio, lower alkylthiadiazolylthio, hydroxyamidino, hydroxyamidino substituted with lower alkoxycarbonyl, and hydrazono substituted with pyridyl; and

R^2 is hydrogen, lower alkyl, hydroxy(lower)alkyl, halo(lower)alkyl, lower alkoxy, lower alkylthio, lower alkylsulfonyl, carbamoyl or cyano, or

R^1 and R^2 are taken together to form a group of the formula :

$$-CH_2-CH_2-CH_2-S-,$$





in which R^5 and R^8 are each hydrogen or lower alkyl,

R^3 is hydrogen or halogen,

R^4 is phenyl substituted with substituent(s) selected from the group consisting of halogen, lower alkyl, lower alkoxy, lower alkoxy(lower)alkoxy, halo(lower)alkoxy,

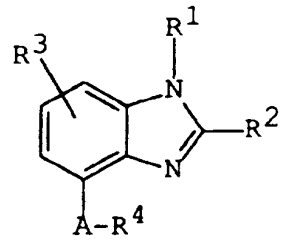
lower alkanoyl, lower alkoxycarbonyl(lower)alkenyl, hydroxy(lower)alkyl and lower alkyldiarylsilyloxy-(lower)alkyl, and

A is $-CON(R^9)-$ or $-N(R^{10})CO-$,

in which R^9 is hydrogen, lower alkyl or lower alkoxycarbonyl(lower)alkyl, and

R^{10} is hydrogen, lower alkyl or lower alkoxycarbonyl(lower)alkyl.

4. A process for preparing a compound of the formula :



wherein

R^1 is acyl, lower alkenyl or lower alkyl optionally substituted with substituent(s) selected from the group consisting of aryl, substituted aryl, a heterocyclic group, a substituted heterocyclic group, hydroxy, substituted hydroxy, cyano, halogen, amino, substituted amino, acyl, mercapto, substituted mercapto, hydroxyamidino, substituted hydroxyamidino and substituted hydrazono, and

R^2 is hydrogen, lower alkyl, hydroxy(lower)alkyl, halo(lower)alkyl, lower alkoxy, lower alkylthio, acyl or

cyano, or

R^1 and R^2 are taken together to form lower alkylene or lower alkenylene, each of which may include O, S or N-R^5 in the chain, in which R^5 is hydrogen or lower alkyl,

R^3 is hydrogen or halogen,

R^4 is a heterocyclic group or aryl, each of which may be substituted with suitable substituent(s), and

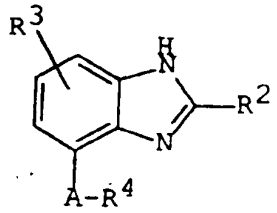
A is $-CON(R^9)-$ or $-NCO(R^{10})-$,

in which R^9 is hydrogen, lower alkyl or substituted alkyl, and

R^{10} is hydrogen, lower alkyl or substituted alkyl,

or its salt, which comprises

a) reacting a compound of the formula :



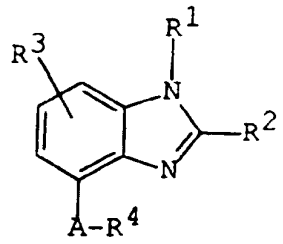
wherein R^2, R^3, R^4 and A are each as defined above, or its salt with a compound of the formula :

$$R^1 - X$$

wherein X is a leaving group, and

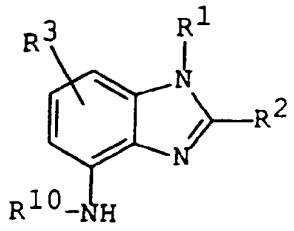
R^1 is as defined above,

or its salt to give a compound of the formula :



wherein R^1, R^2, R^3, R^4 and A are each as defined above, or its salt, or

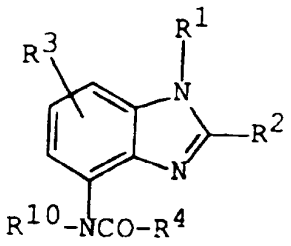
b) reacting a compound of the formula :



wherein R^1, R^2, R^3 and R^{10} are each as defined above, or its reactive derivative at the amino group or a salt thereof with a compound of the formula :

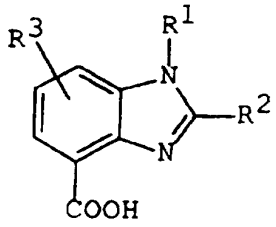
$$R^4 - COOH$$

wherein R^4 is as defined above, or its reactive derivative at the carboxy group or a salt thereof to give a compound of the formula :

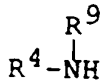


wherein R^1, R^2, R^3, R^4 and R^{10} are each as defined above,
or its salt, or

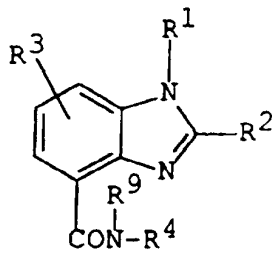
c) reacting a compound of the formula :



wherein R^1, R^2 and R^3 are each as defined above,
or its reactive derivative at the carboxy group
or a salt thereof with a compound of the formula :

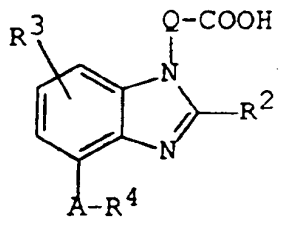


wherein R^4 and R^9 are each as defined above,
or its reactive derivative at the amino group
or a salt thereof to give a compound of the formula :

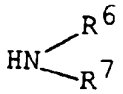


wherein R^1, R^2, R^3, R^4 and R^9 are each as defined above,
or its salt, or

d) reacting a compound of the formula :



wherein Q is lower alkylene, and
R^2, R^3, R^4 and A are each as defined above,
or its reactive derivative at the carboxy group
or a salt thereof with a compound of the formula :

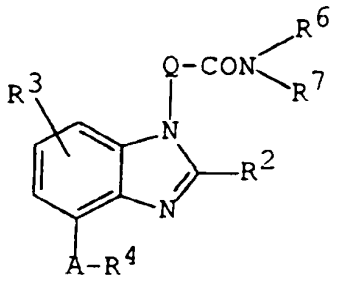


wherein R^6 is hydrogen or lower alkyl optionally substituted with a substituent selected from the group consisting of hydroxy and lower alkoxy, and

R^7 is hydrogen; acyl; lower alkoxy; amino; acylamino; aryl optionally substituted with a substituent selected from the group consisting of lower alkoxy, halo(lower)alkyl and lower alkylamino; a heterocyclic group optionally substituted with a substituent selected from the group consisting of lower alkyl, lower alkoxy, lower alkylthio, halo(lower)alkyl and acyl; or lower alkyl optionally substituted with substituent(s) selected from the group consisting of hydroxy, lower alkoxy, halogen, cyano, acyloxy, acyl, aryl optionally having halo(lower)alkyl and a heterocyclic group optionally having lower alkyl; or

R^6 and R^7 are taken together with the attached nitrogen atom to form a heterocyclic group optionally substituted with a substituent selected from the group consisting of lower alkyl, halogen, aryl and acyl,

or its reacting derivative at the amino group or a salt thereof to give a compound of the formula :



wherein R^2, R^3, R^4, R^6, R^7, A and Q are each as defined above,
or its salt.

5. A pharmaceutical composition comprising a compound of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially nontoxic carrier or excipient.

6. A compound of claim 1 for use as a medicament.

7. A method for the prevention and/or the treatment of bone diseases caused by abnormal bone metabolism which comprises administering a compound of claim 1 to human being or animals.

8. Use of a compound of claim 1 for manufacture of a medicament for the prevention and/or the treatment of bone diseases caused by abnormal bone metabolism.

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/JP 96/02530

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D235/06 A61K31/415 C07D235/08 C07D235/10 C07D235/12
C07D235/24 C07D235/26 C07D235/28 C07D401/06 C07D401/12
C07D403/06 C07D403/12 C07D407/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 03298 A (FUJISAWA PHARMACEUTICAL CO ;SAWADA KOZO (JP); YATABE TAKUMI (JP);) 2 February 1995 see page 51 - page 54; preparations 15-21, 24 see page 78 - page 82; examples 20-26,29 ---	1,5,6
X	EP 0 574 174 A (LILLY CO ELI) 15 December 1993 cited in the application see page 29; example 10 --- -/--	1,5,6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 January 1997	17. 01. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Fink, D

Form PCT ISA 210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/JP 96/02530

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	CHEMICAL ABSTRACTS, vol. 124, no. 21, 20 May 1996 Columbus, Ohio, US; abstract no. 289350a, L.A. FLIPPIN ET AL.: "(R)-3-(6-chloro-1-isopropylbenzimidazole-4-carboxamido)quinuclidine; a high affinity ligand for the (R)-zacopride binding site." page 1326; column 2; XP002022316 see abstract; and Chemical Abstracts, CHEMICAL SUBSTANCE INDEX, vol. 124, 1996, page 2349CS: the compounds with the RN: [175729-69-8], [175729-70-1], [175729-68-7] & BIOORG. MED. CHEM. LETT., vol. 6, no. 4, 1996, pages 477-480, ---	1
P,X	DATABASE WPI Section Ch, Week 9632 Derwent Publications Ltd., London, GB; Class B05, AN 96-318905 XP002022317 & JP 08 143 525 A (BANYU PHARM CO LTD) , 4 June 1996 see abstract ---	1,5-8
A	WO 89 03833 A (HAESSLE AB) 5 May 1989 see the whole document, and in particular: page 13, line 5 -----	1-8

Form PCT ISA 210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 96/02530

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 7 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int onal Application No
PCT/JP 96/02530

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9503298	02-02-95	AU-A-	7195694	20-02-95
EP-A-0574174	15-12-93	AU-B-	661396	20-07-95
		CA-A-	2097460	04-12-93
		CN-A-	1101908	26-04-95
		CZ-A-	9301045	19-01-94
		HU-A-	64330	28-12-93
		JP-A-	6080666	22-03-94
		NO-A-	932004	06-12-93
		NZ-A-	247770	26-10-95
		PL-A-	299177	07-02-94
		US-A-	5556981	17-09-96
		US-A-	5569768	29-10-96
WO-A-8903833	05-05-89	AU-A-	2620388	23-05-89
		EP-A-	0339071	02-11-89
		JP-T-	2501929	28-06-90